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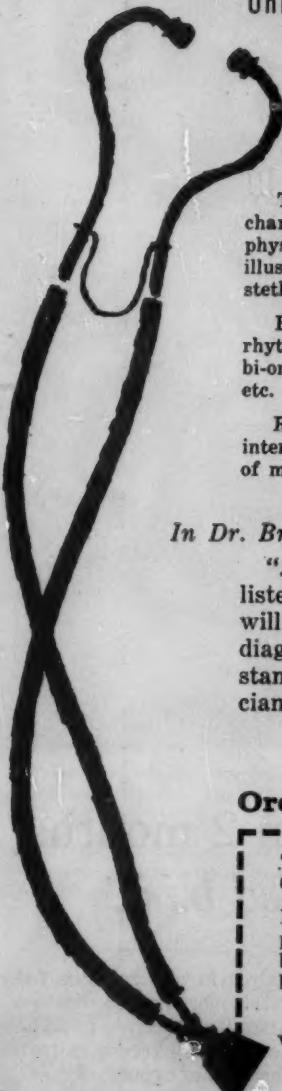
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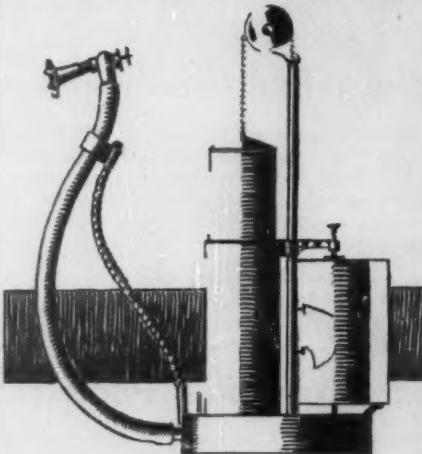
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- 2. Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Am. J. M. Sc. 233:280, March 1957.
- 3. Boyd, L. J., Huppert, V. F., Mulinos, M. G. and Hammer, H.: Am. J. Cardiol. 3:229, Feb. 1959.

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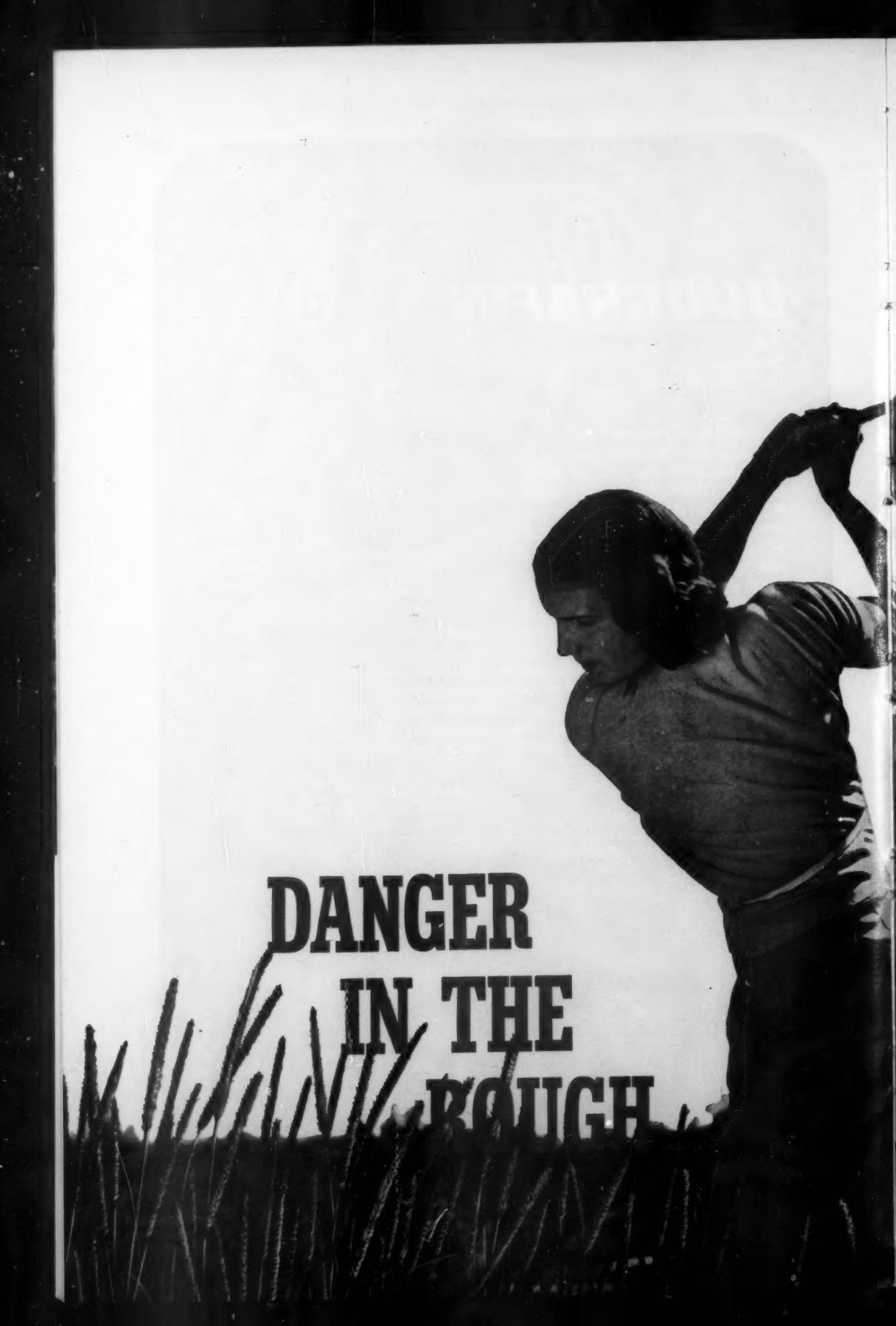
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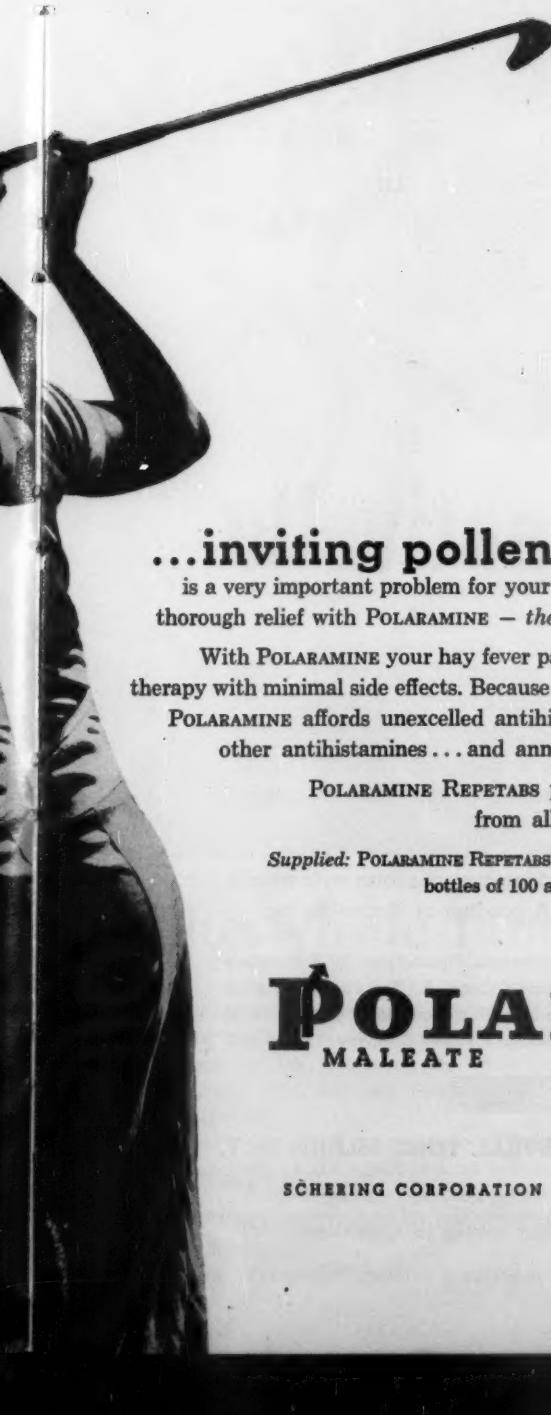
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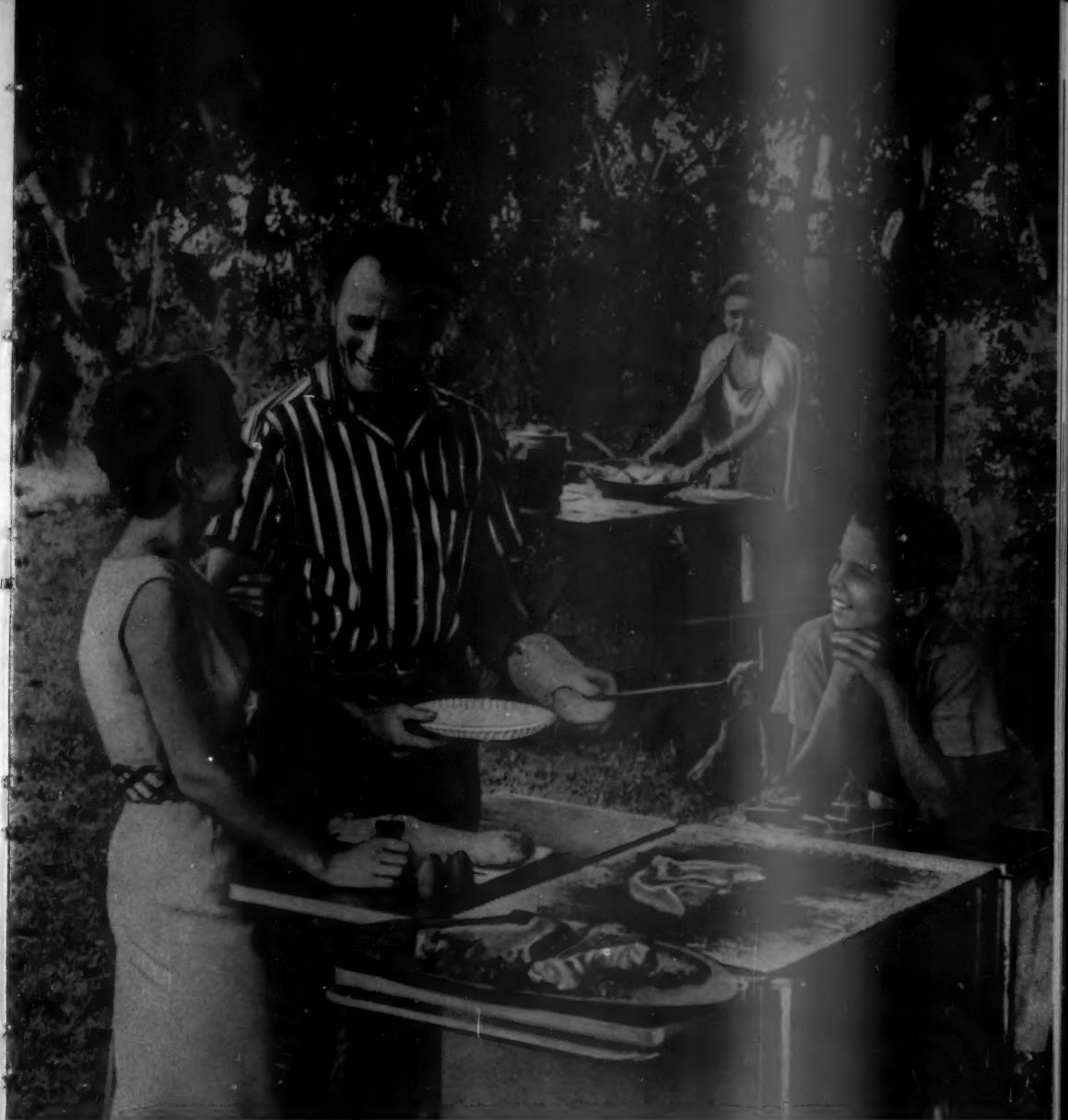
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Kenacort safely starts your patients off right — with all the benefits of systemic corticosteroid therapy and few side effects to worry about. Increased antiallergic, antirheumatic or anti-inflammatory activity is provided on a low dosage schedule.¹⁻³ Clinical improvement is accomplished without water or salt retention,¹⁻⁴ or adverse effect on blood pressure.^{1-3,5} A low sodium diet is not necessary.^{4,5} Gastrointestinal disturbances are negligible^{2,4,5} with less chance of peptic ulcer,⁴ and there is no psychic stimulation to distort the clinical response.¹⁻³ This makes Kenacort particularly valuable in treating your "problem patients" — such as the obese or hypertensive and the emotionally disturbed.

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1. Freyberg, R.H.; Berntsen, C.A., Jr., and Hellman, L.: Arth. & Rheum. 1:215 (June) 1958.
2. Sherwood, N., and Cooke, R.A.: J. Allergy 28:97 (March) 1957.
3. Shelley, W.B.; Harun, J.S., and Pillsbury, D.M.: J.A.M.A. 167:959 (June 21) 1958.
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*KENACORT® IS A SQUIBB TRADEMARK.

SQUIBB



CORT

Squibb Triamcinolone

for all
your allergic
patients
requiring
corticoids

Kenacort, in treating your allergic patients, has proved effective where other steroids have failed. Its potent antiallergic and anti-inflammatory properties provide rapid clinical improvement on a low dosage schedule¹⁻³ with few side effects to worry about.¹⁻⁵ (Kenacort is particularly valuable for your allergic patients with hypertension, cardiac disease, obesity and those prone to psychic disturbances.) In asthma, Kenacort therapy improves ventilation and increases vital capacity.²

Dyspnea and bronchospasm are usually relieved within 48 hours, and sibilant râles often disappear.

Because of its relative freedom from untoward reactions, Kenacort provides corticosteroid benefits to many patients who until now have been difficult to control. Kenacort, too, is indicated in the treatment of arthritis and dermatoses.

SUPPLIES:

Scored tablets of 1 mg. — Bottles of 50

Scored tablets of 2 mg. — Bottles of 50

Scored tablets of 4 mg. — Bottles of 30 and 100

AN AMES CLINIQUICK^{T.M.}

CLINICAL BRIEFS FOR MODERN PRACTICE

Why is the three-day biliary flush recommended after cholecystectomy?

To remove stones and debris frequently present in the common duct when choledochostomy has not been done.

Source: Best, R. R.; Rasmussen, J. A., and Wilson, C. E.: A.M.A. Arch. Surg. 67:839, 1953.

THREE-DAY BILIARY FLUSH*

| | |
|-----------------------|---------------------------------------|
| BEFORE BREAKFAST..... | 6 oz. Citrate of Magnesia |
| AFTER BREAKFAST..... | 3 DECHOLIN with Belladonna tablets |
| BEFORE LUNCH..... | 3 tablespoons pure cream or olive oil |
| AFTER LUNCH..... | 3 DECHOLIN with Belladonna tablets |
| BEFORE SUPPER..... | 3 tablespoons pure cream or olive oil |
| | 1 nitroglycerin tablet (1/100 gr.) |
| | under the tongue |
| AFTER SUPPER..... | 3 DECHOLIN with Belladonna tablets |
| AT BEDTIME..... | 3 DECHOLIN with Belladonna tablets |

*Adapted from Best, R. R., and others: *ibid.*

for hydrocholeresis plus reliable spasmolysis

DECHOLIN® WITH BELLADONNA

(dehydrocholic acid with belladonna, AMES)

in postoperative management—"Hydrocholeretic therapy is employed as a routine feature...in patients with cholecystectomy, cholecystostomy, and other biliary tract procedures."¹

in medical management—"...also recommended for patients with a clinical history of biliary tract disease when gallbladder disease has not been confirmed."²

1. Refresher Article: M. Times 85:1081 (Oct.) 1957.
2. Best, R. R.: Mod. Med. 25:264 (March 15) 1957.

for hydrocholeresis

DECHOLIN®

(dehydrocholic acid, AMES)

Available: DECHOLIN/Belladonna tablets (dehydrocholic acid, AMES) 3½ gr. (250 mg.) and extract of belladonna ½ gr. (10 mg.)
Bottles of 100 and 500.

DECHOLIN tablets: (dehydrocholic acid, AMES) 3½ gr. (250 mg.)
Bottles of 100, 500, and 1,000; drums of 5,000.

AMES

COMPANY, INC
Elkhart • Indiana
Toronto • Canada



71289

ORAL ANTIDIABETIC THERAPY HAS NOT FAILED FOR THIS PATIENT...THANKS TO DIABINESE®

brand of chlorpropamide

The specific pharmacologic properties of DIABINESE — high activity, freedom from metabolic degradation, and gradual excretion — permit (1) prompt lowering of elevated blood sugar levels without a "loading" dose, and (2) smooth, sustained maintenance "devoid of . . . marked blood sugar fluctuations"¹ on convenient, lower-cost, once-a-day dosage. This is the consensus of extensive clinical literature.¹⁻¹¹ Widespread use of DIABINESE since its introduction has confirmed the low incidence of side effects reported by the original investigators.

Thus, DIABINESE merits first consideration for any diabetic presently receiving or potentially better managed with oral therapy — including many diabetics for whom previous oral agents have proved ineffective.

Supplied: Tablets, white, scored 250 mg., bottles of 60 and 250; 100 mg., bottles of 100.

*tablets/once-a-day dosage
effective in 85% of patients who
have become refractory to other
oral agents*



PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.

1. Greenhouse, B.: Ann. New York Acad. Sc. 74:643, 1959. 2. Dobson, H., et al.: *Ibid.*, p. 940. 3. Forsham, P. H.; Magid, G. J., and Dorosin, D. E.: *Ibid.*, p. 672. 4. Beaser, S. B.: *Ibid.*, p. 701; *New England J. Med.* 259:573, 1958. 5. Bloch, J., and Lenhardt, A.: *Ann. New York Acad. Sc.* 74:954, 1959. 6. O'Driscoll, B. J.: *Lancet* 2:749, 1958. 7. Hadley, W. B.; Khachadurian, A., and Marble, A.: *Ann. New York Acad. Sc.* 74:621, 1959. 8. Duncan, G. G.; Schless, G. L., and Demeshkine, M. M. A.: *Ibid.*, p. 717. 9. Handelman, M. B.; Levitt, L., and Calabretta, M. F.: *Ibid.*, p. 632. 10. Hills, A. G., and Abelove, W. A.: *Ibid.*, p. 845. 11. Drey, N. W., et al.: *Ibid.*, p. 962.





For b.i.d. administration

FOR ANXIETY—
PARTICULARLY WHEN EXPRESSED AS APATHY,
LISTLESSNESS AND EMOTIONAL FATIGUE

often effective where other agents fail

*

enthusiastic patient acceptance

*

fast therapeutic response with very low oral doses

*

convenient b.i.d. administration

*

side effects usually slight and transitory

*Trademark

Clinically evaluated, before introduction, in over 12,000 patients

SMITH
KLINE &
FRENCH

UNUSUALLY EFFECTIVE IN RELIEVING ANXIETY IN APATHETIC, EMOTIONALLY FATIGUED PATIENTS

'Stelazine' is a new long-acting psychotherapeutic agent that can help you to bring prompt relief to many of your patients whose anxiety is expressed as apathy, listlessness and emotional fatigue.

Clinical studies in over 12,000 patients have shown that 'Stelazine' is outstanding among agents in its class because it not only relieves agitation and tension, but also *restores normal drive* in many patients who are apathetic due to anxiety.

These studies have also shown that 'Stelazine' is effective in low b.i.d. dosage (2 to 4 mg. daily) and that it is often effective in patients who have failed to respond to meprobamate, prochlorperazine, phenobarbital, mepazine, chlorpromazine, or promazine.

RECOVERY OF NORMAL DRIVE IN APATHETIC PATIENTS

Clinicians report that with 'Stelazine' most apathetic, listless and emotionally fatigued patients regain an alert, more confident outlook. This frequently results in increased mental and physical activity. For example:

Patients' "spirits brightened and initiative and interest picked up considerably in contrast to their pretreatment inertia."¹

'Stelazine' "seemed to have a capacity to restore normal drive in conditions characterized by decreased motor activity and mental apathy."²

ADDITIONAL INFORMATION will reach you by mail or through your S.K.F. representative. We hope you'll decide that 'Stelazine' deserves an early trial. Smith Kline & French Laboratories, Philadelphia.

REFERENCES: 1. Gearren, J.B.: *Dis. Nerv. System* 20:66 (Feb.) 1959. 2. Margolis, E.J., et al.: Scientific Exhibit at 12th Clinical Meeting of the American Medical Association, Minneapolis, Dec. 2-5, 1958. 3. Phillips, F.J., and Shoemaker, D.M.: *ibid.* 4. Ayd, F.J., Jr.: *Clin. Med.* 6:387 (Mar.) 1959. 5. Tedeschi, D.H., et al.: in *Trifluoperazine: Clinical and Pharmacological Aspects*, Philadelphia, Lea & Febiger, 1958, pp. 23-33.

leaders in psychopharmacology

SMITH
KLINE &
FRENCH

CHOKED WITH AIR

IN CHRONIC BRONCHITIS, ASTHMA AND EMPHYSEMA, Choledyl helps the air-choked patient breathe again. Choledyl is often effective where other xanthine preparations fail, because its greater solubility promotes absorption and builds higher blood levels without the gastrointestinal irritation associated with aminophylline. Choledyl allows intensive, effective, day-by-day medication . . . is well tolerated even on prolonged administration. After Choledyl has been given for two weeks, patients usually display a marked reduction in wheezing and coughing—and breathing becomes easier.

CHOLEDYL®

brand of oxtriphylline

bettters breathing... forestalls the crisis



MORRIS PLAINS, N.J.

The response to an antidiarrheal preparation is directly linked to the effectiveness of its adsorbent. In both POLY MAGMA and POLY MAGMA Plain, the new agent Claysorb* gives you a previously unattainable adsorptive power . . . proved to be five times beyond that of kaolin in removing diarrhea-causing toxins. In addition, POLY MAGMA and POLY MAGMA Plain protect the irritated intestinal walls, promote well-formed stools, help restore healthy intestinal function.

Why Claysorb means more effective antidiarrheal treatment

POLY MAGMA

For bacterial diarrhea—
bactericidal against many pathogens

POLY MAGMA Plain

For nonbacterial diarrhea—
same formula but without antibiotics

Polymagma®

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate,
and Pectin with Claysorb* (Activated Attapulgite,
Wyeth) in Alumina Gel

*Trademark

Wyeth
Philadelphia 1, Pa.



for leading respiratory infections
in nursery, hospital and
convalescent patients

DOXIDAN

Restores normal bowel function. Prevents and
cures intestinal dysentery. Restores normal
respiratory physiology. Provides rapid relief
from bronchitis, pneumonia - no bowel disturbance.

Opposite: The abdominal area of a patient with acute appendicitis. Administration of Doxidan relieved him of his pain in less than one hour.

LLOYD BROTHERS, INC.

CINCINNATI 3, OHIO



The Medical Department
of The Purdue Frederick Company
is proud to introduce
to the medical profession

ARTHROPANTM

LIQUID

BRAND OF CHOLINE SALICYLATE, PATENT PENDING

the newest antiarthritic,
anti-inflammatory, analgesic—
without the disturbing
side effects of steroids,
without the dangers of blood
dyscrasias, without the
limitations and discomforts of
usual salicylate therapy.

ARTHROPAN Liquid... "born of a therapeutic need"... The need was for a better antiarthritic agent — an agent free of the therapeutic limitations and the discomforting or potentially dangerous side effects associated with usual therapies... Under development for several years, ARTHROPAN has been studied in several thousand patients by more than 180 investigators and is currently being evaluated in many different disorders... The rapid effectiveness, the comfortable and constant action, and the certain safety of new ARTHROPAN Liquid are established as facts... ARTHROPAN breaks through therapeutic barriers, offering you new vistas in successful therapy of arthritis.

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**FREE YOUR ARTHRITIC PATIENTS FROM THE
DISADVANTAGES OF STEROID / PHENYLBUTAZONE / ASPIRIN THERAPY**



"LIMITATIONS AND DISCOMFORTS OF STANDARD SALICYLATES"

New! **ARTHRO PAN** TM.
LIQUID

BRAND OF CHOLINE SALICYLATE U. S. & FOREIGN PATENTS PENDING

ARTHRO PAN is the new anti-arthritis, anti-inflammatory analgetic agent which assures effective relief of arthritis, without the inherent disadvantages of steroid, phenylbutazone, or standard salicylate therapy. Extensive clinical trials¹ in thousands of patients by more than 180 investigators have demonstrated that ARTHRO PAN is *extremely well tolerated* by virtually all patients—even the 15 to 30 per cent of the arthritic population who experience gastric distress after the required high dosages of aspirin. Administration of high, tolerated dosages of ARTHRO PAN may eliminate, or greatly reduce the need for steroid therapy with its potentially hazardous side effects. ARTHRO PAN is further distinguished by its unusually rapid action—it is *absorbed 5 times faster than aspirin^{2,3,4}*—an important advantage for the arthritic requiring rapid relief of "early morning joint stiffness." Its *high palatability* (cherry-flavored solution) makes it ideal for the arthritic who has difficulty in swallowing a large number of tablets each day.

DOSAGE: Each teaspoonful (5 ml.) contains 870 mgm. of Choline Salicylate. Average dose for adults is 1 teaspoonful 3 to 4 times daily. The dosage may be adjusted upward according to the patient's response and the physician's therapeutic judgment.

SUPPLIED: Bottles of 16 and 8 ounces.

CITED REFERENCES: 1. Complete data available on request to the Medical Director. 2. Wolf, J., Abody, R.: Federation Proc. 18:605, 1959. 3. Broh-Kahn, R. H.: Federation Proc. 18:17, 1959. 4. Smith, E. K.: Personal Communication.



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NEW YORK 14, N.Y. | TORONTO 1, ONTARIO

protects
against
anginal
attacks

eases
cardiac
tension

RUSSEK: PETN is "...
the most effective drug
currently available for
prolonged prophylactic
treatment of angina pectoris."¹ Prevents some
80% of anginal attacks.

RUSSEK: "I favor ATARAX [as
the tranquilizer for the anxious cardiac] . . . because
there is an absence of side-
effects with this drug, and
also because in cardinals who
are troubled with ectopic beats,
ATARAX has a quinidine-like action."²

PETN
(pentaerythritol tetranitrate)



ATARAX
(brand of hydroxyzine)

CARTRAX*

(PETN + ATARAX)

Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX).

For convenience, write "CARTRAX 10" or "CARTRAX 20."

*TRADEMARK

Supplied: In bottles of 100.

References: 1. Russek, H. I.: Postgrad. Med. 19: 562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1956.



New York 17, N. Y.

Division, Chas. Pfizer & Co., Inc.

Science for the World's Well-Being

for full corticosteroid benefits
new **Gammacorten**

...a potent, highly effective corticosteroid;
profound anti-inflammatory activity, with min-
imal potential for corticosteroid side effects



**this arthritic
needed
Gammacorten**

How this arthritic—and others—responded to GAMMACORTEN is shown on the following pages

With **GAMMACORTEN**, a full measure of corticosteroid benefit can now be brought to patients who have heretofore obtained less than optimal benefit from adrenocortical therapy. In practice, the increased activity of **GAMMACORTEN** means maximal mobility for the arthritic; maximal freedom from attack for the asthmatic; rapid and complete resolution of lesions for the dermatologic patient. Unwanted adrenocortical effects are relatively infrequent with **GAMMACORTEN**. Should side effects occur, they can be usually managed by reducing dosage or by supplemental measures.

Photographs used with permission of patients.

these arthritics needed Gammacorten

PATIENT W. M., 42, has had rheumatoid arthritis since September 1955. Previous treatment included prednisone. Considerable soreness, pain and stiffness, particularly in shoulders, hands and elbows. Major complaint was pain in the hands. There was swelling in the finger joints, with ulnar deviation of the hands and slight contracture of the elbows.



BEFORE GAMMACORTEN: W. M. cannot flatten hand on table; finger joints extremely swollen; he could not move his hands without pain.



ONE WEEK AFTER GAMMACORTEN: W. M. can flatten hand without pain; swelling is considerably reduced. Measurement of grip shows increased hand strength.



BEFORE GAMMACORTEN: Patient J. D., 58, had arthritis since 1935. Previous treatment included prednisone. At time of examination, shoulder, arm, and finger joints were frozen. J. D. could not button his shirt or perform other functions without help. He had pain all the time. Hands were badly deformed. Unable to move arms away from body; shoulders appeared frozen.



ONE WEEK AFTER GAMMACORTEN: J. D. has shown remarkable improvement; was able to raise arms to shoulder level without incurring pain.



ONE WEEK AFTER GAMMACORTEN: Fingers, although permanently deformed, have regained some usefulness; can button jacket, extract cigarette and strike match.

Gammacorten^{T.M.}
(dexamethasone CIBA)

CIBA
SUMMIT, N.J.

8/2701 MM-1

for full corticosteroid benefits: new Gammacorten

this arthritic needed Gammacorten

PATIENT M. S., age 81, at time of first visit was in severe pain and very uncomfortable. Complained of swelling of wrists, legs, various joints; there was pain and stiffness in cervical area and lower spine; pain, swelling and limited motion in the fingers; slight ulnar deviation of the hand. He could not raise his arms above the level of his shoulders.

Treatment and Result: After 36 hours of GAMMACORTEN therapy, M. S. had "complete relief." Joint swelling had decreased, pain was almost absent, range of motion had increased dramatically. At the end of the first week of GAMMACORTEN he was free of discomfort and able to return to his job as a porter.

BEFORE GAMMACORTEN: M. S. demonstrates the position necessary to put on his hat (range of motion was so restricted that he could not comb his hair).



BEFORE GAMMACORTEN: His fingers were extremely painful and were so swollen that a size 11 jeweler's ring would not fit over his small finger.



BEFORE GAMMACORTEN: Hands were so painful, stiff and swollen that M. S. could not flatten hand or extend fingers on flat surface.



AFTER ONE WEEK OF GAMMACORTEN: M. S. could put on his hat normally, could comb hair; function near-normal at end of first week of treatment.



AFTER ONE WEEK OF GAMMACORTEN: Size 11 jeweler's ring passes easily over previously swollen joint. At end of first week, "puffiness" had virtually disappeared.



AFTER ONE WEEK OF GAMMACORTEN: Pain completely subsided. M. S. can flatten hand, extend fingers and flex in normal manner without pain.

Photographs used with permission of patient.

How to use Gammacorten

in arthritis — An initial dosage of 1.5 to 3 mg. per day (2 to 4 tablets divided into 3 or 4 doses). This dosage should be continued until a satisfactory symptomatic response is obtained—usually within 3 or 4 days. After a favorable response has been obtained, reduce dosage by 1/3 every 2 to 3 days until either maintenance dosage is established or therapy can be discontinued. Satisfactory control can often be maintained with as little as 0.75 mg. to 1.5 mg. per day.

in asthma and allergy—IN STATUS ASTHMATICUS: Initial daily dosage of GAMMACORTEN is 7.5 to 10 mg. (10 to 13 tablets divided into 3 or 4 doses). As soon as the acute state is controlled, reduce dosage slowly by 1/3 to 1/4 until a satisfactory maintenance level is reached or until therapy is discontinued.

IN CHRONIC BRONCHIAL ASTHMA: Initial dosage is 1.5 to 3 mg. of GAMMACORTEN per day (2 to 4 tablets divided into 3 or 4 doses). After a satisfactory response has been obtained, decrease dosage by 1/3 every 2 to 3 days until either maintenance level has been determined or therapy can be discontinued. Asthmatics can often be maintained for long periods on as little as 0.75 mg. to 1.5 mg. of GAMMACORTEN daily.

IN INTRACTABLE HAY FEVER: Start with 2 to 3 mg. (3 to 4 tablets divided into 3 or 4 doses) of GAMMACORTEN per day. Symptoms should be promptly relieved; prolonged maintenance therapy is unnecessary for these self-limiting disorders.

in skin disorders — Start with 2 to 3 mg. (3 to 4 tablets divided into 3 or 4 doses) of GAMMACORTEN daily. Satisfactory control is usually obtained at this dosage level. In chronic conditions, dosage should be decreased by 1/3 every 2 to 3 days until either a satisfactory maintenance level has been achieved or therapy can be discontinued. In acute or self-limiting disorders, treatment may be discontinued as soon as control has been obtained.

SUPPLIED: GAMMACORTEN Tablets, 0.75 mg.

2/5708 MK-2

Gammacorten^{T.M.}

(dexamethasone CIBA)

...a potent, highly effective corticosteroid;
profound anti-inflammatory activity, with minimal potential for corticosteroid side effects



BEFORE GAMMACORTEN: M. S. could not raise arms above shoulder level; even the degree of motion shown was extremely painful.



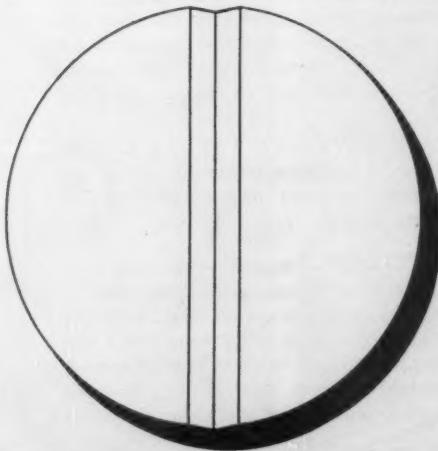
AFTER ONE WEEK OF GAMMACORTEN: Range of motion and rotation dramatically increased; M. S. could move arms without pain for the first time in months.

CIBA

SUMMIT, N.J.

GREATER CONVENIENCE DOUBLE POTENCY

AT LOW COST TO YOUR PATIENT



new convenient oral tablets

PENTIDS '400,' each scored tablet contains 400,000 units of penicillin G potassium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units.

also available

PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 100, and 500.

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose bottles.

PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and 500.

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, vials of 12 and bottles of 100.

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple sulfas per tablet, bottles of 30, 100, and 500.

Squibb® is a Squibb trademark

Pentids '400'

Squibb 400,000 units Buffered Penicillin G Potassium Tablets

For the treatment of penicillin susceptible infections—ranging from mild to moderately severe—due to hemolytic streptococcus / pneumococcus / staphylococcus / and for the prevention of streptococcal infections where there is a history of rheumatic fever

Clinical effectiveness confirmed by millions of cases

Specific in many common infections

Daily dosage may be spaced without regard to mealtime

Ease of administration with oral penicillin

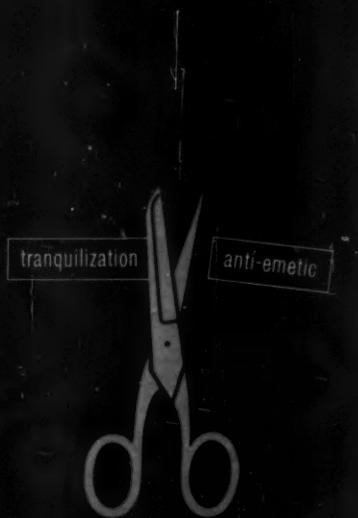
Economy for the patient

SQUIBB



Squibb Quality—the Priceless Ingredient

now potent tranquilizer therapy is safer than ever



Actual freedom of Mellaryl from major toxic effects is due to greater specificity of tranquilizing action—it is freed from such "side-line" effects as anti-emetic action.

MELLARIL is virtually free
of such toxic effects as
 • jaundice
 • Parkinsonism
 • blood dyscrasias

Thioridazine [MELLARIL] is as effective
as the best available phenothiazine, but
with appreciably less toxic effects than
those demonstrated with other phenothia-
zines.^{1,2} This drug appears to represent
a major addition to the safe and effective
treatment of a wide range of psycho-
logical disturbances seen daily in the
clinics or by the general practitioner.³



Mellaril®

THIORIDAZINE
specific tranquilizer • safer at all dosage levels

remarkable lack of side effects

In more than 3,000 carefully-followed patients, Mellaril has been almost completely free of such major side effects as jaundice, extrapyramidal symptoms, Parkinsonism, blood dyscrasias, dermatitis—even when given in quantities far in excess of the usual dosage.

"POVERTY" OF SIDE EFFECTS

"The most striking aspect of thioridazine [Mellaril] therapy is the poverty of side effects.... In its lack of side effects and low toxicity, it is superior to all other tranquilizing drugs tested. For this reason also it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication because of dizziness, sleepiness, increased tension or parkinsonism with other drugs."²

NEGLIGIBLE SIDE EFFECTS

"Side effects were negligible at all dosage levels: no incidence of parkinsonism or other extrapyramidal symptoms. Minimal sedation, on the whole lower than with other tranquilizing agents. No alteration in liver function, urine or blood. No photosensitivity. Patient acceptability was exceptional: lack of drowsiness, lethargy or 'washed out' feeling, permitted patients to carry on normal everyday activities. Orthostatic hypotension was absent. The initial 'keyed up' tense feeling common to other drugs of this type was absent.... Patients forced to interrupt treatment with other phenothiazine derivatives because of parkinsonism or other extrapyramidal symptoms were able to continue therapy with thioridazine without appearance of parkinsonism."³

SINGULARLY FREE OF SIDE EFFECTS

"The extrapyramidal syndrome was not encountered in

any of its forms. Dizziness and sleepiness responded to a reduction in dosage. Other side effects did not occur.... It is singularly free from the side effects ordinarily seen with these [phenothiazine] compounds."⁴

ABSENCE OF SIGNIFICANT SIDE EFFECTS

"None of the following toxic effects, so common after administration of the phenothiazines, was present during the period of Thioridazine administration: Parkinsonism or Parkinson-like symptoms, photosensitivity, orthostatic hypotension, bone-marrow depression."¹

MINIMAL SIDE EFFECTS

"Side effects such as extrapyramidal activity, jaundice and photosensitivity have not been observed in patients treated with Thioridazine [Mellaril]. Extrapyramidal side effects produced by other phenothiazines have disappeared promptly with no deterioration in the behavioral response when these patients have been shifted to Thioridazine."⁵

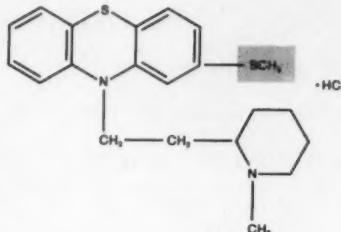
NO JAUNDICE

"No allergic reactions were observed such as skin eruptions, jaundice or agranulocytosis. Central nervous system toxicity, as manifested by extrapyramidal effects, seizures, and excitement did not occur despite the use of high doses (up to 2000 mg.) of the drug."⁶

Mellaril®
THIORIDAZINE HCl
Specific, effective tranquilizer • Safer at all dosage levels



a new advance in tranquilization:
greater specificity of tranquilizing action plus fewer side effects



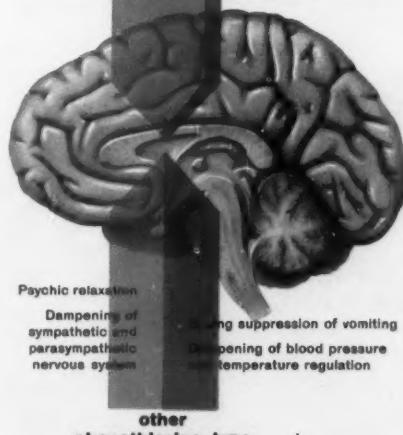
Of 109 phenothiazines synthesized by Sandoz, Mellaryl was selected as the most promising on the basis of extensive evaluation. The presence of a thiomethyl radical ($S-CH_3$) in the position conventionally occupied by a halogen in other phenothiazines is unique and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

MELLARYL

PSYCHIC RELAXATION

DAMPENING OF
SYMPATHETIC AND
PARASYMPATHETIC
NERVOUS SYSTEM

Minimal suppression of vomiting
Little effect on blood pressure
and temperature regulation



- 1 A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.
- 2 Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.
- 3 A notable absence of extrapyramidal stimulation.
- 4 Lack of impairment of patient's normal drive and energy, while achieving psychomotor control in mental and emotional disorders.
- 5 Virtual freedom from toxic effects — jaundice, photosensitivity, skin eruptions, disturbed body temperature regulation, blood forming disorders have been absent in reports currently available.

These properties add up to a greater margin of safety in general office practice, in ambulatory psychiatric out-patient clinics, and in hospitalized patients.

Mellaril®

PHENOTHIAZINE
ANTI-EMETIC TRANQUILIZER
SPECIFICALLY DESIGNED FOR LOW Dose Usage Levels

excellent clinical response

In office practice and in hospitalized patients, Mellaril has proved highly useful for a wide variety of major and minor emotional disorders (such as anxiety, tension, apprehension, alcoholism, agitated psychoneurosis, agitated psychotic states, etc.).

EXTREMELY SATISFACTORY ". . . produced extremely satisfactory results in the broad therapeutic range represented in this series."³

POTENT AGENT ". . . appears to be a potent agent in the symptomatic management of a variety of psychiatric states."⁴

MAJOR ADDITION TO THERAPEUTICS "This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."¹

AN ACTIVE AGENT "Thioridazine is an active therapeutic agent. . . . It is effective in a variety of psychiatric disorders, including schizophrenic reactions. . . . The drug is particularly advantageous for a group of schizophrenic patients who are sometimes made worse by other phenothiazine derivatives or Rauwolfia alkaloids. It should also be suitable for treating patients with psychoneuroses and chronic brain syndrome."⁶

EVEN IN VERY SEVERE CASES "Of the 152 patients treated 25 have been released and they have not suffered a relapse. This proportion is significant if we stop to consider that we are dealing only with acute cases which had been considered hopeless and obviously destined to finish their days in an asylum."⁷

EXCELLENT THERAPEUTIC RESPONSE "Patients with emotional tensions resulting from the stress and strain of life . . . were treated with Mellaril at the dosage level of 10 mg. three times daily.
In 94 such patients, 83 obtained an excellent therapeutic response."⁸

Mellaril®
THIOPRIMINE HCl

specific, effective tranquilizer • safer at all dosage levels



"...extremely satisfactory results..."
 in a clinical spectrum ranging from
 minor nervous disorders to
 severe psychotic disturbances³

RESULTS WITH MELLARIL IN 194 PATIENTS³

ACUTE PSYCHOTICS

83% satisfactory effect

Some cases had complete remission of symptoms. Most were able to return home to useful occupations.

CHRONIC PSYCHOTICS

68% satisfactory effect

Relief of symptoms in cases permitted easier management and a return to a more or less useful life.

NEUROTICS

57% satisfactory effect

Some cases, complete relief of symptoms. Other cases, partial relief of symptoms.

RESULTS WITH MELLARIL IN PATIENTS PREVIOUSLY TREATED WITH OTHER TRANQUILIZERS³

| DIAGNOSTIC CATEGORY | IMPROVED % | VERY SATISFACTORY % | SATISFACTORY % | UNSATISFACTORY % |
|---------------------------------|------------|---------------------|----------------|------------------|
| SCHIZOPHRENIA | | | | |
| Acute | 89 | 61 | 28 | 11 |
| Chronic paranoid | 84.2 | 31.6 | 52.6 | 15.8 |
| Chronic, other | 73.9 | 21.7 | 52.2 | 26.1 |
| Residual | 57.1 | 9.5 | 47.6 | 42.9 |
| CHRONIC BRAIN SYNDROME | 66.6 | 33.3 | 33.3 | 33.3 |
| CHRONIC PSYCHONEUROSIS | 62.5 | 12.5 | 50 | 37.5 |
| CHRONIC PSYCHOSOMATIC DISORDERS | 75 | 25 | 50 | 25 |

Mellaril®
 THIODIAZINE HCl
 specific, effective tranquilizer • safer at all dosage levels



a guide to administration and dosage

Dosage ranges from 10 mg. three or four times a day in milder situations to 25 mg. three or four times a day for more disturbed patients. In ambulatory psychiatric out-patients, dosages of 50 to 100 mg. three or four times a day have been found adequate. For severely dis-

turbed hospitalized psychotics, dosages of 200 to 300 mg. three times a day may be administered.

Dosage must be individualized according to the condition and degree of response. In all cases, the smallest effective dosage should be determined for each patient.

| INDICATION | USUAL STARTING DOSE | TOTAL DAILY DOSAGE RANGE |
|---|---------------------|--------------------------|
| ADULTS | | |
| Mental and Emotional Disturbances: | | |
| MILD — where anxiety, apprehension and tension are present | 10 mg. t.i.d. | 20-60 mg. |
| MODERATE — where agitation exists in psychoneurosis, alcoholism, intractable pain, senility, etc. | 25 mg. t.i.d. | 50-200 mg. |
| SEVERE — in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.: | | |
| Ambulatory | 100 mg. t.i.d. | 200-400 mg. |
| Hospitalized | 100 mg. t.i.d. | 200-800 mg. |
| CHILDREN | | |
| BEHAVIOR PROBLEMS IN CHILDREN | 10 mg. t.i.d. | 20-40 mg. |

PRECAUTIONS: Although possessing a unique structure and a selectivity of action which broadens its therapeutic ratio, the physician should be alert to the possibility of untoward reactions in certain susceptible individuals. In

particular, he should watch for potential hemopoietic depression, jaundice or orthostatic hypotension. As with other phenothiazines, Mellaril is contraindicated in severely depressed or comatose states from any cause.

SUPPLIED: MELLARIL Tablets, 10 mg., 25 mg., 100 mg. Bottles of 100.

1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. Kinross-Wright, V. J.: Lecture, Clinical Meeting, American Medical Association, Minneapolis, Dec. 4, 1958. 3. Kinross-Wright, V. J.: Scientific Exhibit, Clinical Meeting, American Medical Association, Minneapolis, Dec. 2-5, 1958. 4. Cohen, S.: TP-21, a new phenothiazine, Am. J. Psychiat. 115:356, Oct. 1958. 5. Glick, B.: Scientific Exhibit, American Psychiatric Association, Philadelphia, April 27-May 1, 1959. 6. Hollister, L. E., and Macdonald, B. F.: Presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959. 7. Remy, M.: Schweiz. med. Wchnschr. 88:1221, Nov. 29, 1958. 8. Freed, S. C., in discussion on Thioridazine (Mellaril) in Psychiatric Patients, Hollister, L. E., and Macdonald, B. F., presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959.

- controls neurotic and psychotic patients with anxiety, apprehension, nervous tension
- virtual absence of jaundice, parkinsonism, photosensitivity, dermatitis
- minimal sedation and drowsiness
- does not mask organic conditions such as brain tumors, intestinal obstruction, etc., because of lack of anti-emetic action
- increased specificity of action results in greater safety at all dosage levels



Mellaril®

THIOPRIMIN HCl
Effectively effective therapeutic range at low dosage levels



HYPERTENSION

"When chlorothiazide is used, lower and, hence, less toxic dosages of other antihypertensive agents become effective in controlling blood pressure. Chlorothiazide does not reduce blood pressure in normotensive subjects, although the drug induces the same increase in salt excretion."

Freis, E.D.: J.A.M.A. 189:105, (Jan. 10) 1959.

Dosage: One 250 mg. tablet DIURIL b.i.d. to one 500 mg. tablet DIURIL t.i.d.

DIURIL®

CHLOROTHIAZIDE

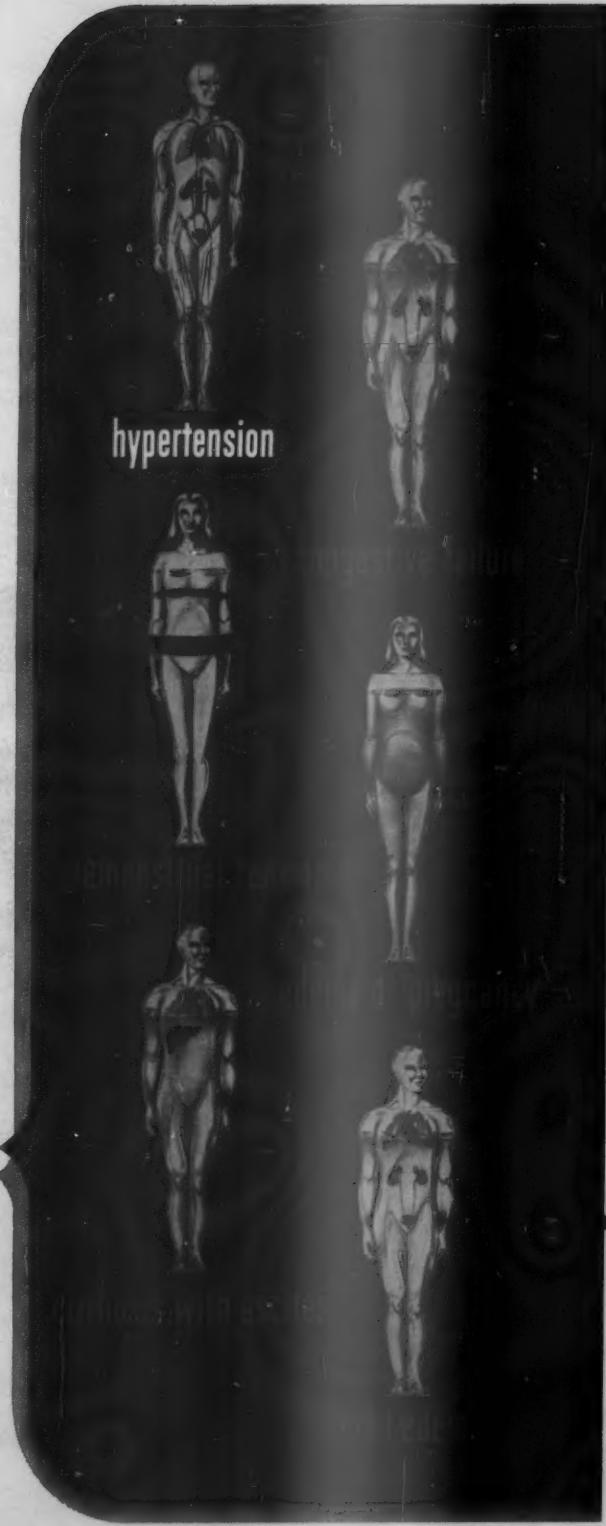
a continuing
and consistently
outstanding record
of safety and
efficacy in:

Supplied: 250 mg. and 500 mg. scored tablets DIURIL (Chlorothiazide). DIURIL is a trademark of Merck & Co., Inc. Additional information is available to the physician on request.



MERCK SHARP & DOHME
Division of Merck & Co., Inc., Philadelphia 1, Pa.

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TO BE SPECIFIC, DOCTOR

for nausea • vomiting • vertigo **BONAMINE***

brand of meclizine hydrochloride

Clinically proved relief up to 24 hours with a single dose

BONAMINE (a non-phenothiazine) is remarkably free of side effects

BONAMINE HAS NO KNOWN CONTRAINDICATIONS-CAN BE USED WITH CONFIDENCE FOR AS LONG OR AS OFTEN AS REQUIRED

BONAMINE Tablets, scored, 25 mg. Boxes of 8, bottles of 100 and 500.

BONAMINE Elixir, cherry flavored, 12.5 mg. per 5 cc. Bottles of one pint.

BONAMINE Chewing Tablets, pleasantly mint flavored, 25 mg. Packages of 8.

DOSAGE: Usually 25 to 50 mg. once a day.



PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, N.Y.

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Science for the world's well-being **Pfizer**

Now
in inflammatory anorectal disorders . . .

The Promise of Greater Relief

the first suppository to contain
hydrocortisone for effective control of proctitis

- Proctitis accompanying ulcerative colitis
- Radiation proctitis
- Postoperative scar tissue with inflammatory reaction
- Acute and chronic nonspecific proctitis
- Acute internal hemorrhoids
- Medication proctitis
- Cryptitis



Ulcerative Colitis



Radiation Proctitis



Postoperative
Scar Tissue

Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

Wyanoids® HC

Rectal Suppositories with Hydrocortisone, Wyeth



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NEW
from
Mead
Johnson

a myo-



-vascular relaxant

VASODILAN®

Pronounced VA-ZO-DY-LAN

Isoxsuprine hydrochloride, Mead Johnson

Mead Johnson is proud to announce the availability of VASODILAN, an unusual new compound with myo-vascular relaxant action. The unique myo-vascular action of this substance is manifested by selective relaxant effects on smooth muscle of the peripheral and cerebral vascular beds and of the uterus.

A major indication for VASODILAN is in the symptomatic treatment of peripheral vascular disease.

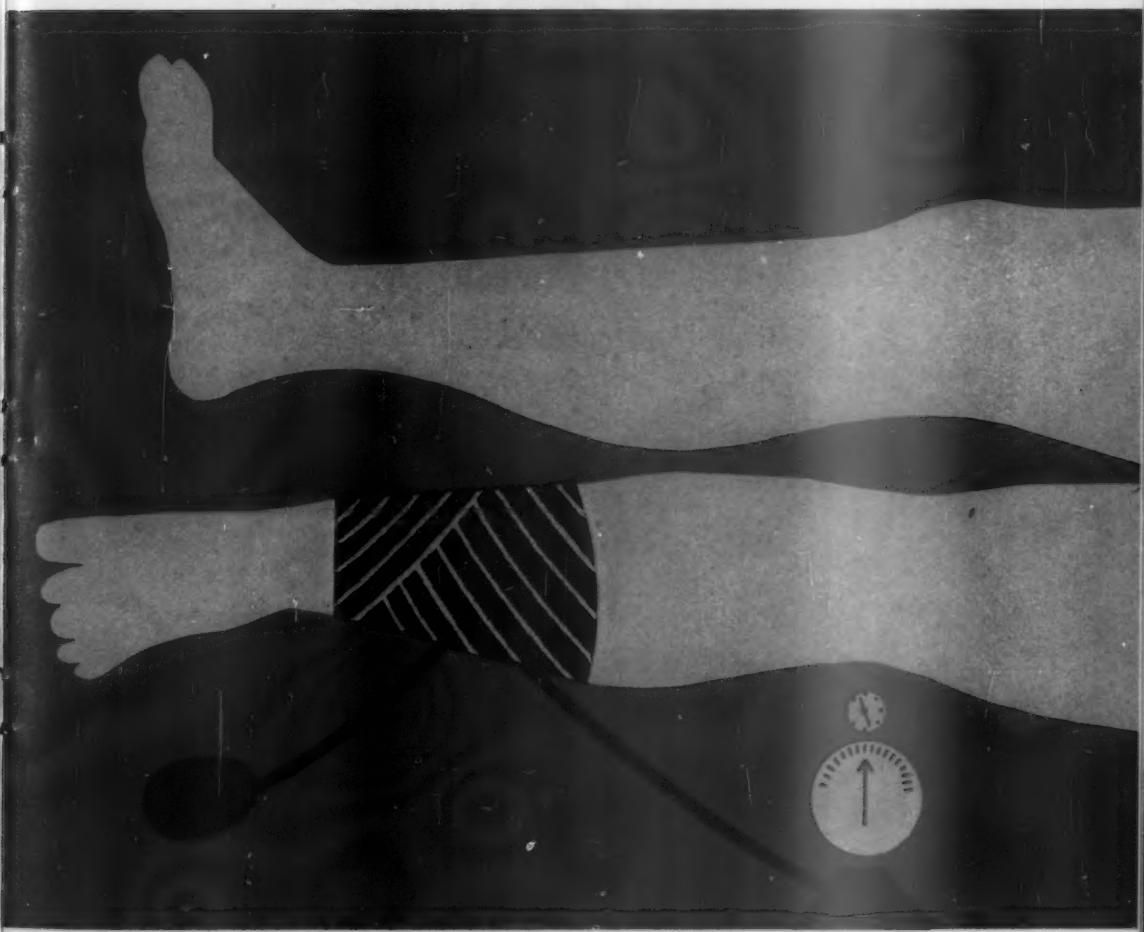
selective peripheral action to relieve symptoms of arterial insufficiency¹—
intermittent claudication
leg pain
coldness and numbness of extremities in
Arteriosclerosis Obliterans
Diabetic Vascular Disease
Buerger's Disease
Thrombophlebitis

brings blood to the deep tissues by direct action on the arterial wall¹⁻³
with remarkable safety in recommended doses
without adverse effects on coronary flow^{1,2}
without troublesome hypotension or tachycardia^{1,2}
without renal effects^{1,2}
without increase in gastric acidity²
without ganglionic blocking action¹⁻³
without development of tolerance¹

Available as VASODILAN Tablets, 10 mg., bottles of 100.
VASODILAN Injection, Ampuls, 2 cc. (5 mg./cc.), boxes of 6.

Oral Dosage: 10 or 20 mg. (1 or 2 tablets) three or four times a day. For complete details on indications, dosage, administration and clinical background of VASODILAN, see the brochure on this product available on request from Mead Johnson and Company, Evansville 21, Indiana.

Bibliography: (1) Kaindl, F.; Samuels, S. S.; Selman, D., and Shaftel, H.: Angiology, to be published. (2) Kaindl, F.; Pärlan, J., and Polsterer, P.: Wien. klin. Wchnschr. 68:186, 1956. (3) Brücke, F., et al.: Wien. klin. Wchnschr. 68:183, 1956.



Mead Johnson
Symbol of service in medicine

Why G.I. patients abandon therapy

Bandes¹ reports that G.I. patients often abandon therapy because of the unpleasant side effects of the prescribed drugs—blurred vision, dry mouth and loginess.

In a clinical trial of such patients who had abandoned other therapy, 90% had gratifying relief of symptoms, and 85% were free of *any* side effects on

Milpath[®]

[®]Miltown + anticholinergic

Direct antispasmodic action, plus control of anxiety and tension, provide rapid, safe relief of pain, spasm and anxiety—without the side effects of belladonna, bromides or barbiturates.

FORMULA: Each scored tablet contains: meprobamate 400 mg., tridihexethyl chloride 25 mg. (formerly supplied as the iodide).

DOSAGE: 1 tablet t.i.d., with meals, and two at bedtime.

1. Bandes, J.: Combined Drug Therapy in Gastrointestinal Disturbances; Increased benefit through diminished side reactions, Am. J. Gastroenterology, 30:600, Dec. 1958.



WALLACE LABORATORIES New Brunswick, N.J.

If your patient has
high blood pressure
plus one or more of
these complications:
anxiety
congestive failure
tachycardia
edema/overweight
control all the
symptoms with just
one prescription

new **Esidrix-Serpasil®**
(hydrochlorothiazide
and reserpine CIBA)
Combination Tablets

new Esidrix-Serpasil:



High blood pressure plus tachycardia

Therapy: Esidrix-Serpasil. *Rationale:* Heart-slowng effect of Serpasil to prolong diastole, allow more time for recovery of myocardium, increase coronary blood flow, improve cardiac efficiency. Potentiated antihypertensive effect for greater blood pressure control.



High blood pressure plus congestive failure

Therapy: Esidrix-Serpasil. *Rationale:* Potent diuretic action of Esidrix to relieve edematous condition, improve cardiac status. Combined antihypertensive action of Esidrix and Serpasil for lowest blood pressure levels. Convenience of combination tablet medication for greater patient acceptance.

one prescription that controls high blood pressure plus its complications



B.P.: 220/140 mm. Hg
Edema
Weight: 210 pounds



B.P.: 170/112 mm. Hg
Nervous
Sweating palms

High blood pressure plus edema/overweight

Therapy: Esidrix-Serpasil. *Rationale:* Diuretic effect of Esidrix to eliminate excess body fluids, bring patient to dry weight. Potentiated antihypertensive effects of Esidrix and Serpasil in combination. Convenience of 1-prescription therapy.

High blood pressure plus anxiety

Therapy: Esidrix-Serpasil. *Rationale:* Central action of Serpasil to calm the patient, shield him from environmental stress. Combined antihypertensive action of Esidrix and Serpasil for lowest blood pressure levels. Simplified dosage schedule.

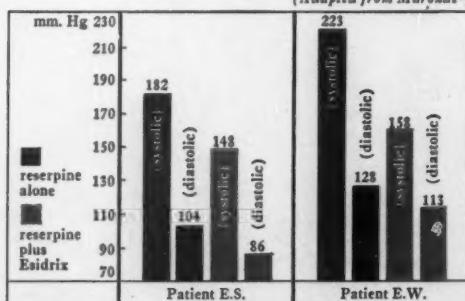
one prescription that controls high blood pressure plus its complications Esidrix-Serpasil Combination Tablets

*A new antihypertensive combination—*Esidrix-Serpasil is a combination of **ESIDRIX^{T.M.}** (hydrochlorothiazide CIBA), an improved analog of chlorothiazide developed by CIBA research, and **SERPASIL[®]** (reserpine CIBA). Each tablet combines the potent diuretic and mild antihypertensive effects of Esidrix with the antihypertensive, heart-slowing and calming effects of Serpasil.

*Indications—*Esidrix-Serpasil is indicated in all grades of hypertension, particularly when one or more of the following complications exist: anxiety, tachycardia, congestive failure, pitting edema, edema of obesity, other edematous conditions.

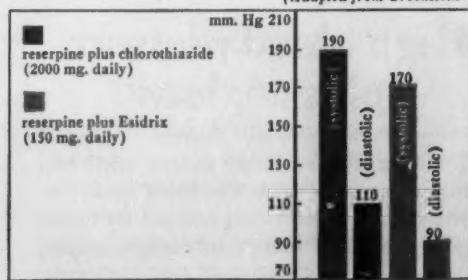
*More effective than either drug alone—*Investigators who have used the combination of hydrochlorothiazide and reserpine report that it is more satisfactory than either drug alone.

(Adapted from Maronde¹)



*More effective than chlorothiazide-reserpine combinations—*Many patients resistant to chlorothiazide-reserpine therapy have shown significant clinical response when Esidrix-Serpasil was started. The blood pressure of patient shown below was only slightly reduced on chlorothiazide and reserpine. When Esidrix was substituted for chlorothiazide, lower blood pressure levels were achieved.

(Adapted from Greenstein²)



*Dosage—*Esidrix-Serpasil is administered orally in a dosage range of 1 to 4 tablets daily. Each tablet contains 25 mg. of Esidrix and 0.1 mg. of Serpasil. The total daily dose may be given after breakfast or in 2 or 3 divided doses. Dosage in every case should be individualized and adjusted to meet changing needs.

Since the antihypertensive effect of Serpasil is not immediately apparent, the maximal reduction in blood pressure may not occur for 2 weeks. At this time the dosage of Esidrix-Serpasil should be adjusted to the amount necessary to obtain the desired blood pressure response. For maintenance, as little as 1 tablet daily may be sufficient.

In cases of more severe hypertension, dosage of Esidrix-Serpasil can be revised upward to 4 tablets daily. When necessary, more potent antihypertensive agents such as Apresoline, Ecolid or other ganglionic blockers may be added. As Esidrix-Serpasil potentiates the action of other antihypertensive drugs, such additions to the regimen should be gradual and effects carefully observed. When Esidrix-Serpasil is started in patients already receiving ganglionic blockers, such as Ecolid, dosage of the latter should be immediately reduced by at least 50 per cent.

*Side effects and cautions—*As when any diuretic agent is used, patients should be carefully observed for signs of fluid and electrolyte imbalance. Esidrix in therapeutic doses is generally well tolerated. Side effects, even from large doses, have been few. Since Esidrix greatly reduces the amount of Serpasil needed, the incidence of side effects sometimes encountered with Serpasil is diminished.

Complete information on Esidrix-Serpasil available on request.

*Supplied—*Esidrix-Serpasil Tablets, 25 mg./0.1 mg., each containing 25 mg. of Esidrix and 0.1 mg. of Serpasil; bottles of 100.

*References—*1. Maronde, R. F.: Clinical Report to CIBA.
2. Greenstein, S.: Clinical Report to CIBA.

APRESOLINE[®] hydrochloride (hydralazine hydrochloride CIBA)

ECOLID[®] chloride (chlorisondamine chloride CIBA)

new **Esidrix^{T.M.}**
Serpasil[®]
(hydrochlorothiazide
and reserpine CIBA)
Combination Tablets

CIBA
SUMMIT, N. J.

*Ann Woodward,
Director*

Of Course You Can't "Take It Easy"!



But you can extend the benefits of your skill and experience without extending yourself beyond reasonable limits. Many other busy physicians have demonstrated the success of the plan which you, also, may desire to adopt: delegate some of your responsibilities to an associate whom you have (1) carefully selected; (2) proved competent by thorough induction into your methods.

The Woodward Bureau gives swift, systematic service in helping physicians to find associates who measure up. Many fine men in all fields of medicine announce their availability through our channels, and our background of over fifty years in professional placement has alerted us to careful interpretations of individual needs.

Whether your requirements are on a permanent or temporary basis we are prepared to assist you fully.

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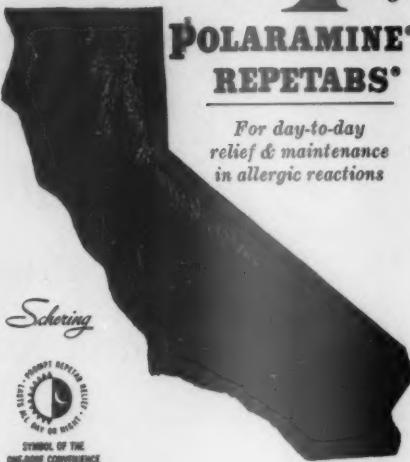
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the medical profession serving medicine
with distinction over half a century.

wherever the 4 winds blow

new 4 mg.

POLARAMINE® REPETABS®

For day-to-day
relief & maintenance
in allergic reactions



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Muscle
Spasm

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Brand of Orphenadrine HCl

An energizing agent against weakness and fatigue... effective as a euphoriant... counteracts sialorrhea and oculogyria... lessens rigidity and tremor... well tolerated... even in presence of glaucoma.

in Low-Back Pain



Effective relief from spasm and pain in painful skeletal muscle disorders due to sprains, strains, herniated intervertebral disc, whiplash injuries, chronic osteoarthritis... No known contraindications.

DOSAGE: Usually 1 tablet 50 mg. t.i.d.



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Northridge,
California

*Trademark of Brodhead-Sherman & Pharmacal
Pharmaceutical Company, Inc., St. Louis, Missouri

NOW

*... a new way
to relieve pain
and stiffness
in muscles
and joints*

INDICATED IN:

MUSCLE STIFFNESS

LUMBOSACRAL STRAIN

SACROILIAC STRAIN

WHIPLASH INJURY

BURSITIS

SPRAINS

TENOSYNOVITIS

FIBROSITIS

FIBROMYOSITIS

LOW BACK PAIN

DISC SYNDROME

SPRAINED BACK

"TIGHT NECK"

**TRAUMATIC STRAINS
AND BRUISES**

**POSTOPERATIVE
MYALGIA**



- Exhibits unusual analgesic properties, different from those of any other drug
- Specific and superior in relief of somatic pain
- Modifies central perception of pain without abolishing natural defense reflexes
- Relaxes abnormal tension of skeletal muscle

SOMA^{T.M.}

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

- More specific than salicylates
- Less drastic than steroids
- More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. **SOMA** is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with **SOMA** than with any previously used analgesic, sedative or relaxant drug.

SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of **SOMA** is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.
Literature and samples on request.



WALLACE LABORATORIES, NEW BRUNSWICK, N. J.

because it "most closely approaches the 'ideal anticoagulant,'"

COUMADIN
become
accepted
anticoagulant of choice

"most of the drawbacks
of Dicumarol have been
overcome [with COUMADIN] ... It is
my firm belief that in time it
will replace Dicumarol on the
basis of its performance
over a wide variety of
conditions..."²

has
widely
as the

COUMADIN®

ORAL
I.V. or I.M.
SODIUM

IN MYOCARDIAL INFARCTION AND OTHER THROMBOEMBOLIC DISORDERS

After more than five years' clinical experience, it has been concluded: "In my opinion, Warfarin sodium [COUMADIN] is the best anticoagulant available today."³

COUMADIN CONSISTENTLY PROVIDES

rapid and sustained effect with low dosage • high predictability • ease of control for long periods • low incidence of "escape" • equal effectiveness by oral or parenteral routes • reduced need for frequent prothrombin time determinations after initial dosage adjustment • ready reversibility with vitamin K₁

Complete Information and Reprints on Request



ENDO LABORATORIES
Richmond Hill 18, New York

TABLETS

For oral administration—2 mg., lavender, scored; 5 mg., peach, scored; 10 mg., white, scored; 25 mg., red, scored.

INJECTION

For parenteral administration—Single Injection Units, consisting of one vial, 75 mg., and one 3-cc. ampul Water for Injection.

AVERAGE DOSE

Initial, 50 mg. Maintenance, 5-10 mg. daily, as indicated by prothrombin time determinations.

COUMADIN (warfarin) Sodium—manufactured under license from the Wisconsin Alumni Research Foundation—developed for clinical use by Endo.

References: 1. Baer, S., et al.: J.A.M.A. 167:704, 1958. 2. Link, K. P.: Circulation 19:97, 1959. 3. Meyer, O. O.: Postgrad. Med. 24:110, 1958.

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private Spa under
conservative medical
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HOMESTEAD
HOT SPRINGS, VIRGINIA

M. B. Jarman, M.D., Medical Director



potentiation • efficacy • toleration

broad-spectrum antibiotic therapy

COSA-TERRAMYCIN®
oxytetracycline with glucosamine

| | | |
|----------|------------------|------------------|
| capsules | oral suspension | pediatric drops |
| 125 mg. | peach flavored, | peach flavored, |
| 250 mg. | 125 mg. per ten- | 100 mg. per cc. |
| | spoonful (5 cc.) | (5 mg. per drop) |
| | 2 oz. bottle | 10 cc. bottle |
| | | (with calibrated |
| | | dropper) |

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B & O

BELLADONNA & OPIUM • FORMULAS 15A-16A

SUPPRETTES®

SUCCESSOR TO THE SUPPOSITORY

Effective narcotic therapy rectally

For over 50 years Belladonna and Opium Formulas 15A and 16A have provided quick systemic relief of severe pain without side effects. The Belladonna alkaloids are in amounts sufficient to oppose the objectionable side effects of opium, especially the morphine alkaloid. These formulations are now available in Webster's water-soluble NEOCERA® base which breaks down on contact with moisture of the mucous membrane, not temperature. No refrigeration is necessary.

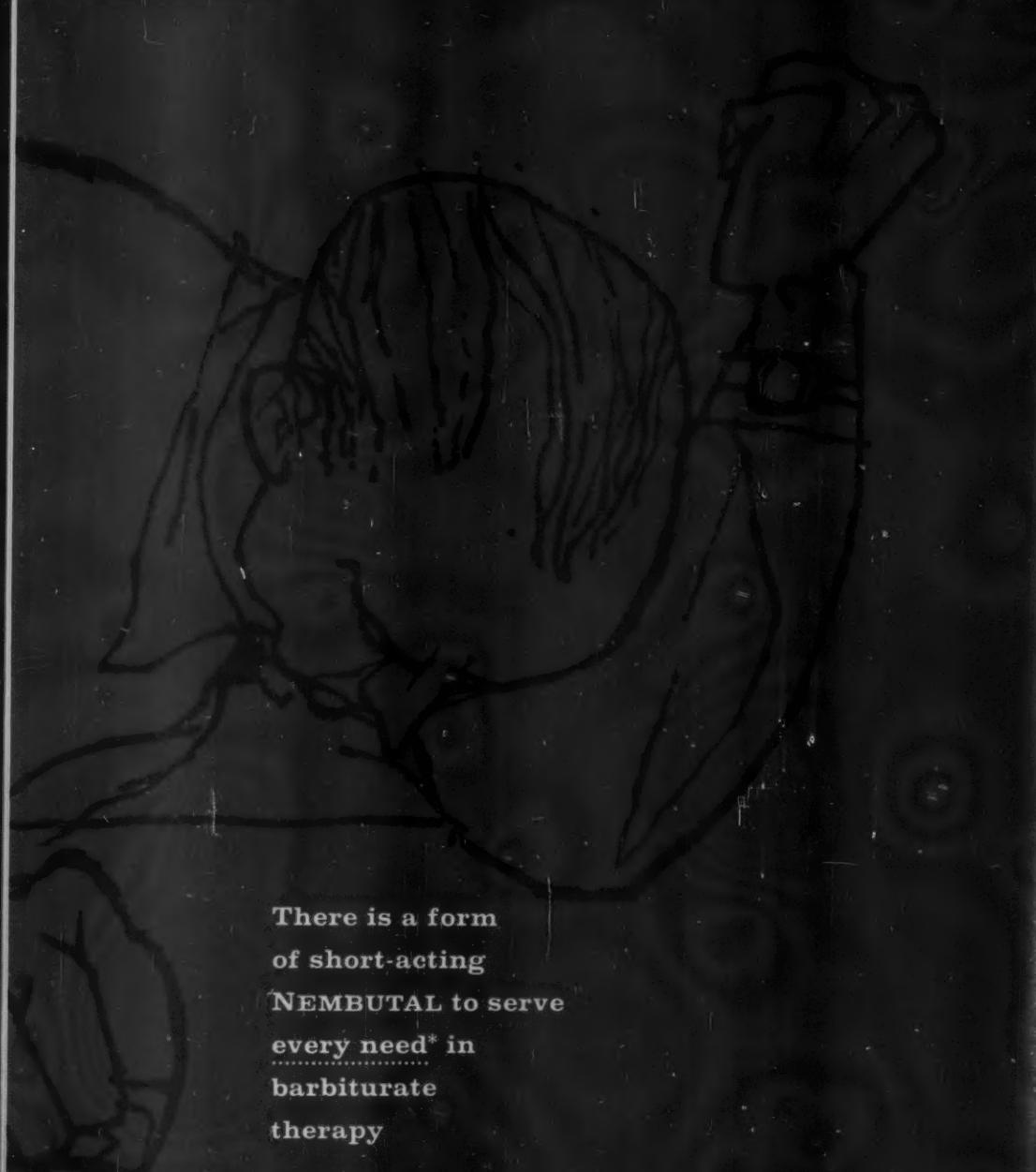
Composition: Each 15A Suprette contains $\frac{1}{2}$ gr. Powdered Opium, U.S.P.— $\frac{1}{4}$ gr. Extract Belladonna—Each 16A Suprette contains 1 gr. Powdered Opium, U.S.P.— $\frac{1}{4}$ gr. Extract Belladonna
Packaged 12 Supprettes to the jar. *Narcotic Order Required.



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OUR 50TH ANNIVERSARY OF PHARMACEUTICAL MANUFACTURE



There is a form
of short-acting
NEMBUTAL to serve
every need* in
barbiturate
therapy

*In controlling excited states

NEMBUTAL®

(Pentobarbital, Abbott)

Capsules, Tablets, and Injectable Formulations

Abbott

"...safely, comfortably, and effectively useful in initial digitalization, redigitalization and maintenance digitalization of patients in heart failure."*



Rheumatic Heart Disease

GITALIGIN^{®†}

WIDEST SAFETY MARGIN—AVERAGE THERAPEUTIC DOSE ONLY $\frac{1}{3}$ THE TOXIC DOSE.‡

FASTER RATE OF ELIMINATION THAN DIGITOXIN OR DIGITALIS LEAF.

THESE SIMPLE DOSAGE EQUIVALENTS MAKE IT EASY TO SWITCH YOUR PATIENT TO GITALIGIN—0.5 mg. of Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.5 mg. digoxin or 0.1 mg. digitoxin.

Supplied:

GITALIGIN 0.5 mg. Tablets—bottles of 30 and 100.

GITALIGIN Injection Ampuls—2.5 mg. in 5 cc. sterile, I.V. solution.

GITALIGIN Drops 30 cc. bottle with special calibrated dropper.



WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

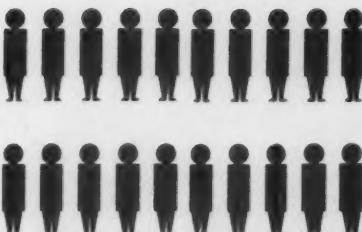
FOR UNMATCHED TOLERANCE AND OPTIMAL ABSORPTION

MOL-IRON VITAMIN C

(Molybdenized-Ferrous Complex)

IN IRON DEFICIENCY ANEMIA - SPECIALLY WHEN IRON ABSORPTION IS DEFECTIVE

MOL-IRON...
WELL TOLERATED
by **97.9%**
of 336 patients¹⁻⁹



But 22.4%
G. I. side
effects
with
 FeSO_4

VITAMIN C—"Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid..."¹⁰



Each contains - Mol-Iron (ferrous sulfate) 195 mg., and molybdenum oxide 3 mg.) plus ascorbic acid 75 mg. Bottles of 100.
Dose - 1 or 2 tablets t.i.d.

1. Brit. M. J. 1:407, 1952. 2. Bull. Margaret Hague Mat. Hosp. 1:68, 1946. 3. Am. J. Obst. & Gyn. 57:541, 1949. 4. Connecticut M.J. 14:988, 1950. 5. J. Lancet 66:218, 1946. 6. Am. J. Obst. & Gyn. 62:947, 1951. 7. Ann. J. Med. Sc. 212:76, 1946. 8. Ober. & Gynec. 5:201, 1955. 9. J. Ped. 41:170, 1952. 10. Ann. Int. Med. 42:458, 1955.

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WHITE LABORATORIES, INC.
KENILWORTH, NEW JERSEY

gout

ANTURAN^{T.M.}

(sulfapyrazone GEIGY)

High Potency Uricosuric Agent

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosuric agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecid[†]...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is good.

Clinically, ANTURAN:

- Prevents formation of new tophi
- Causes gradual absorption of old tophi
- Relieves chronic pain
- Restores joint mobility

ANTURAN is not designed for the treatment of acute attacks for which BUTAZOLIDIN[®] is recommended. Detailed Information On Request.

YU, T. F.; Burns, J. J., and Gutman, A. B. Arth. & Rheumat. 1:532, 1958.
ANTURAN[™] (sulfapyrazone GEIGY). Scored tablets of 100 mg. in bottles of 100.

BUTAZOLIDIN[®] (phenylbutazone GEIGY).

Ardsley, New York

in India, it's called 'Delhi belly'



diarrhea by any name

GASTROENTERITIS
BACILLARY DYSENTERY
PARADYSENTERY
SALMONELLOSIS
DIARRHEA OF THE NEWBORN
NONSPECIFIC DIARRHEA
"SUMMER COMPLAINT"

usually responds rapidly to

Cremomycin®

NEOMYCIN-SULFASUXIDINE®-KAOLIN-PECTIN SUSPENSION

for rapid relief of virtually all diarrheas

*fruit-flavored, readily accepted by patients of all ages**

Neomycin — rapidly bactericidal against most intestinal pathogens, but is relatively ineffective against such diarrhea-causing organisms as Shigella.

SULFASUXIDINE® — an ideal adjunct to neomycin because it is highly effective against Shigella and certain other neomycin-resistant organisms.

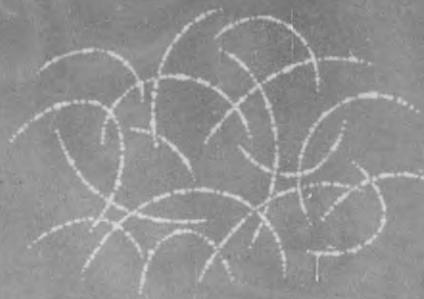
Kaolin and Pectin — coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

*For infants, CREMOMYCIN may be administered in the regular bottle feeding since its fine particles easily pass through a standard nursing nipple.



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CREMOMYCIN AND SULFASUXIDINE (SUCCINYL SULFATHIAZOLE) ARE TRADEMARKS OF MERCK & CO., INC.



Used in every type of practice
and clinical specialty today,
EQUANIL® (meprobamate, Wyeth)
has proved that anxiety and
tension *can* be controlled to
smooth the course of diagnosis,
treatment, and convalescence.
Anxiety is a fact of life. Anx-
iety is a fact of illness.



can be given **LONGER...**



24-25
JANUARY

THURSDAY
12

THURSDAY
15
JANUARY

MONDAY
19
JANUARY

TUESDAY
20
JANUARY

FRIDAY
6
FEBRUARY

MONDAY
19
JANUARY

FRIDAY
3
JANUARY

WEDNESDAY
18
MARCH

21

JANUARY

WEDNESDAY
28
JANUARY

MONDAY
16
JANUARY

MONDAY
23
JANUARY

MONDAY, January 19, 1959

31-1
JANUARY

MONDAY
23
JANUARY

14-15
MARCH

MONDAY
3
JANUARY

MONDAY
10
JANUARY

MONDAY
17
JANUARY

MONDAY
24
JANUARY

MONDAY
31
JANUARY

MONDAY
7-8
MARCH

MONDAY
14
JANUARY

MONDAY
21
JANUARY

MONDAY
28
JANUARY

MONDAY
4-5
MARCH

MONDAY
11
JANUARY

MONDAY
18
JANUARY

MONDAY
25
JANUARY

MONDAY
1
JANUARY

Saturday, Jan. 24, 1959

Sunday, Feb. 1

Tuesday, February 3, 1959

Wednesday, February 4, 1959

Thursday, February 5, 1959

Friday, February 6, 1959

Saturday, February 7, 1959

Sunday, Feb. 8

...MUCH LONGER

...IN URINARY
TRACT INFECTIONS.

"Thiosulfil" is the one sulfa compound that can be given safely, successfully, and effectively, without interruption over prolonged periods of time.¹⁻⁵

"Thiosulfil"

BRAND OF SULFAMETHIZOLE

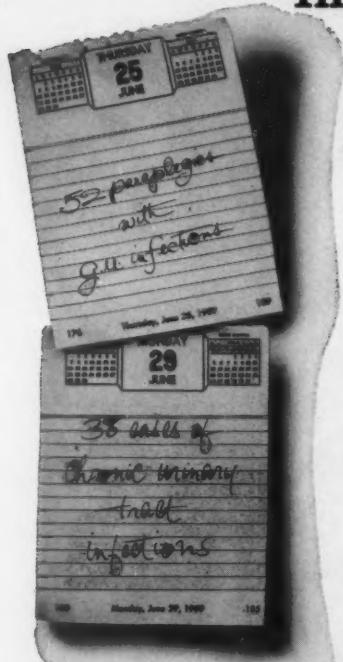
clinical proof and bibliography on following page



AYERST LABORATORIES

New York 16, N.Y. • Montreal, Canada

In Urinary Tract Infections



"Thiosulfil" ...for prolonged use

"Thiosulfil" is a highly soluble sulfonamide derivative which can be administered effectively over a long period of time with minimal toxic manifestation."

- Cottrell, T.L.C.; Rolnick, D., and Lloyd, F. A.: *Rocky Mountain M.J.* 56:66 (Mar.) 1959.

"It [Thiosulfil] is useful for palliation in chronic urinary tract infections that are due to pathological conditions which cannot be cured. The drug can be taken over a long period of time with practically no untoward side reactions."

- Barnes, R. W.: *J. Urol.* 71:655 (May) 1954.



"Thiosulfil" ...well tolerated

"Thiosulfil" was remarkably well tolerated, there being no discontinuation of therapy due to untoward effects, and very few mild reactions were noted. . . . Thiosulfil is a very valuable adjuvant in the treatment of common urinary infections . . ."

- Bourque, J. P. and Joyal, J.: *Canad. M.A.J.* 68:337 (Apr.) 1953.

"Thiosulfil" ...safe, effective

"Clinical trial appears to indicate that the drug [Thiosulfil] can be tolerated where other sulfa drugs cannot and that it is effective where some others are not. . . . The drug has been given with good results in the presence of urinary retention and severe uremia."

- Goodhope, C. D.: *J. Urol.* 72:552 (Sept.) 1954.

Continued from preceding page



"Thiosulfil" ...potent antibacterial agent

... "Thiosulfil" is an effective chemotherapeutic agent in urinary tract infections....there was only one failure in the "Thiosulfil" treated acutely infected group (31 patients)."

- Hughes, J.; Coppridge, W. M., and Roberts, L. C.: South. M.J. 47:1082 (Nov.) 1954.

In difficult cases of paraplegics with urinary tract infections, "Thiosulfil" was ineffective in only 7 per cent [93% effective] of the urinalyses as contrasted to 28 per cent [72% effective] of the urines on [sulfisoxazole] therapy."

- Cottrell, T. L. C.; Rolnick, D., and Lloyd, F. A.: Rocky Mountain M.J. 56:66 (Mar.) 1959.

"Thiosulfil" delivers more therapeutic impact at site of infection than any other single or combined sulfa compound. Higher urinary concentrations are achieved. 98% of the drug is present as free, active (nonmetabolized) sulfa... a most efficient sulfa drug with outstanding patient toleration.⁴

- Boger, W. P.: The Antibacterial Sulfonamides: Comparative Studies, Scientific Exhibit Section, American Academy of General Practice Eleventh Annual Scientific Assembly, April 6-9, 1959, San Francisco, California.

"Thiosulfil"®

BRAND OF SULFAMETHIZOLE

Usual dosage: Adults, two tablets or two teaspoonfuls q.i.d.

Supplied: Tablets: No. 785 — 0.25 Gm. per tablet (Scored). Bottles of 100 and 1,000.

Suspension: No. 914 — 0.25 Gm. per 5 cc. (teaspoonful). Bottles of 4 and 16 fluidounces.

also available: "Thiosulfil"-A

BRAND OF SULFAMETHIZOLE WITH PHENYLALO-DIAMINO-PYRIDINE HCl
in urinary tract infection when analgesia is desired

"Thiosulfil"-A — each tablet contains:
0.25 Gm. sulfamethylthiadiazole and 50 mg.
phenylalo-diamino-pyridine HCl.

Usual dosage: Adults, two tablets q.i.d.

Supplied: Tablets: No. 784 — Bottles of 100 and 1,000.



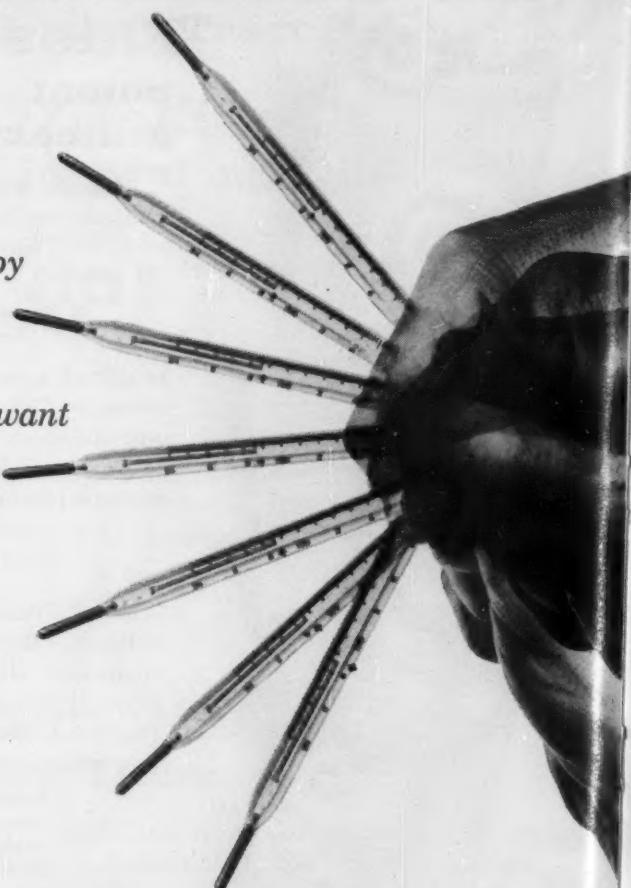
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New York 16, N.Y. • Montreal, Canada

in oral penicillin therapy

the speed of action you want

the reliability you need



Penicillin, still the most frequently prescribed antibiotic, assumes new reliability in the form of PEN-VEE K. Tablet or Liquid PEN-VEE K may be prescribed for all infections responsive to oral penicillin . . . *including many usually treated with parenteral penicillin.*

The speed of action and reliability of oral potassium penicillin V have been dramatically demonstrated by recent studies^{1,2} in which 107 subjects were each given 400,000 units of the antibiotic. Appreciable penicillin levels were consistently produced within 15 minutes; peak levels within one-half hour. Penicillin levels still persisted in all subjects at two hours, and in 93 per cent of subjects at four hours.

1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. 5:139 (Feb.) 1958.

PEN-VEE® K 

Philadelphia 1, Pa.

Liquid: Penicillin V Potassium for Oral Solution;

Tablets: Penicillin V Potassium, Wyeth

SUPPLIED: Liquid: raspberry-flavored, 125 mg. (200,000 units) per 5-cc. teaspoonful; peach-flavored, 250 mg. (400,000 units) per 5-cc. teaspoonful. Both supplied as vials of powder to make 40 cc. Tablets: 125 mg. (200,000 units) and 250 mg. (400,000 units) in vials of 36.

Uneventful Recovery

the pattern of

GLUCOSAMINE-POTENTIATED TETRACYCLINE therapy

COSA-TETRACYN*

capsules
125 mg., 250 mg.
oral suspension
orange flavored, 2 oz. bottle,
125 mg. per teaspoonful (5 cc.)
pediatric drops
orange flavored, 10 cc. bottle
(with calibrated dropper), 5 mg.
per drop (100 mg. per cc.)

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Division, Chas. Pfizer & Co., Inc.
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*Trademark for glucosamine-potentiated tetracycline

NOTE: Rapid and high initial antibiotic blood levels are an important factor in uneventful recoveries. Glucosamine potentiation provides the fastest, highest tetracycline levels available with oral therapy. Bibliography and professional information booklet available on request.

NOW - YOU CAN PRESCRIBE THE UNSURPASSED ADVANTAGES OF

*superior antiallergic efficacy
with new low dosage*

NEW
Aristo

- combines the anti-inflammatory, antiallergic and antihistaminic effects of two agents—ARISTOCORT and chlorpheniramine which, separately, have been proved highly effective in the treatment of allergy
- permits greater latitude in adjusting dosage to minimum level needed for maintenance, because ARISTOCORT and chlorpheniramine are supplied in the lowest dose tablets available for each component alone
- supplies ascorbic acid for increased demand in stress conditions

Indications: Generalized pruritus of allergic origin; hay fever, allergic rhinitis, perennial asthma, seasonal and perennial rhinitis, vasomotor rhinitis; drug reactions and other allergic conditions.

Dosage: One to eight capsules a day in divided doses. Dosages should be established on the basis of individual therapeutic response.

Precautions: Drowsiness may occur, and is usually due to the antihistamine effect. Occasionally this may also cause vertigo, pruritus and urticaria. Because of the low dosage, side effects with ARISTOMIN have been relatively infrequent and minor in nature. However, since ARISTOCORT Triamcinolone is a highly potent glucocorticoid with profound metabolic effect, all precautions and contraindications traditional to cortico-

steroid therapy should be observed. Discontinuance of therapy must not be sudden after patients have been on steroids for prolonged periods. It must be carried out gradually over a period of as much as several weeks.

Further information available on request.

Supply: Each ARISTOMIN Capsule contains:

| | |
|---------------------------------|--------|
| ARISTOCORT® Triamcinolone | 1 mg. |
| Chlorpheniramine Maleate | 2 mg. |
| Ascorbic Acid | 75 mg. |

Bottles of 30 and 100

References: 1. Maurer, M. L.: Clinical Report, cited with permission. 2. Levin, L.: Clinical Report, cited with permission. 3. Gaillard, G. E.: Clinical Report, cited with permission.

ARISTOCORT IN ANTIHISTAMINE COMBINATION

Aristomin®

Steroid-Antihistamine Compound LEDERLE



(Lung x 65, Injected with carbon-gelatin)



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N.Y.

*comments by
clinical investigators:*

"I would conclude that ARISTOMIN is truly a worthwhile aid in treating allergic problems."¹

"The results have been uniformly good. The patients have stated that their symptoms were very much relieved. I have not encountered any side reactions except from one patient, who complained of some drowsiness, which I attribute to the antihistamine."²

"In general . . . it [ARISTOMIN] is an excellent product. Over-all, it appears to be more effective than any simple antihistamine we have used. Despite the fact that we employed it in the treatment of a variety of nonselected individuals and problems, we had excellent and good results in 25 of the 39 patients."³

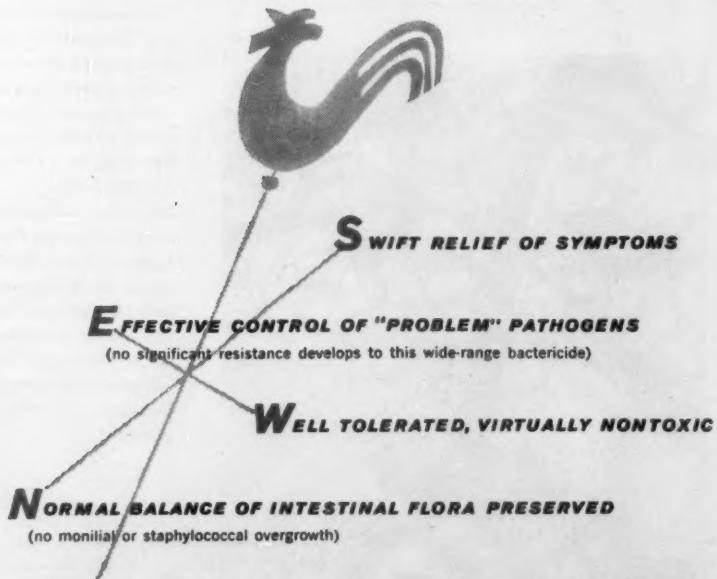
TO STOP DIARRHEA

from all points... growing evidence favors

FUROXONE®

brand of furazolidone

- Pleasant-flavored LIQUID, 50 mg. per 15 cc. (with kaolin and pectin)
- Convenient TABLETS, 100 mg.
- Dosage—400 mg. daily for adults, 5 mg./Kg. daily for children (in 4 divided doses).



From a Large Midwestern University: FUROXONE Controls Antibiotic-Resistant Outbreak. An outbreak of bacillary dysentery due to *Shigella sonnei* was successfully controlled with FUROXONE after a broad-spectrum antibiotic had proved inadequate. Cure rates (verified by stool culture) were 87% with FUROXONE, 36% with chloramphenicol. Only FUROXONE "failures" were those lost to follow-up. Chloramphenicol failures subsequently treated with FUROXONE responded without exception. FUROXONE was also used effectively as prophylaxis and to eliminate the carrier state. It was "extremely well tolerated in all 191 individuals who received it either prophylactically or therapeutically."

Galsota, W. R., and Moranville, B. A.: Student Medicine (in press)

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS

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dosage problem with
muscle relaxants?
no problem with

PARAFLEX®

Chlorzoxazone®

just 6 tablets daily is an
average effective dose

Benefits of a 1- or 2-tablet dose persist for about 6 hours, relieving pain and stiffness and improving function in musculoskeletal disorders such as low back syndrome, sprains, strains, myalgia, fibrositis, and stiff neck. Side effects are rare, almost never require discontinuance of therapy.

Supplied: Tablets, scored, orange, bottles of 50.
Each tablet contains PARAFLEX, 250 mg.



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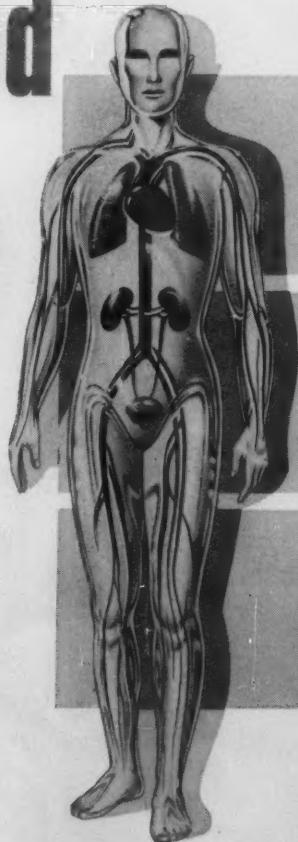
* U.S. Patent Pending

NEW

HYDRODIURILTM

(HYDROCHLOROTHIAZIDE)

simplifies* and
improves any
regimen for
hypertension



*it's as easy as 1, 2, 3 to use

HYDRODIURIL

(HYDROCHLOROTHIAZIDE)

1 Initiate therapy with HYDRODIURIL: one 25 mg. tablet or one 50 mg. tablet once or twice a day. HYDRODIURIL by itself often causes an adequate drop in blood pressure over a period of two to three weeks. This may be all the therapy some patients require.

2 Add or adjust other agents as required: HYDRODIURIL enhances the activity of all commonly-used antihypertensive agents; thus, the dosage of other medication (rauwolfia, reserpine, hydralazine, veratrum) should be initiated or adjusted as indicated by patient condition. If a ganglion-blocking agent is contemplated or being used, usual dosage must be reduced by 50 per cent.

3 Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.

Supplied: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) bottles of 100 and 1,000. Additional literature for the physician is available on request.

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Sinaxar®

a specific
skeletal muscle
relaxant

Chemically unlike any other muscle relaxant, Sinaxar is

- consistently effective in the majority of cases
- long acting: no fleeting effects
- purely a skeletal muscle relaxant . . . free of adverse physical or psychic effects frequently encountered with tranquilizers

DOSAGE: Two tablets three or four times daily.

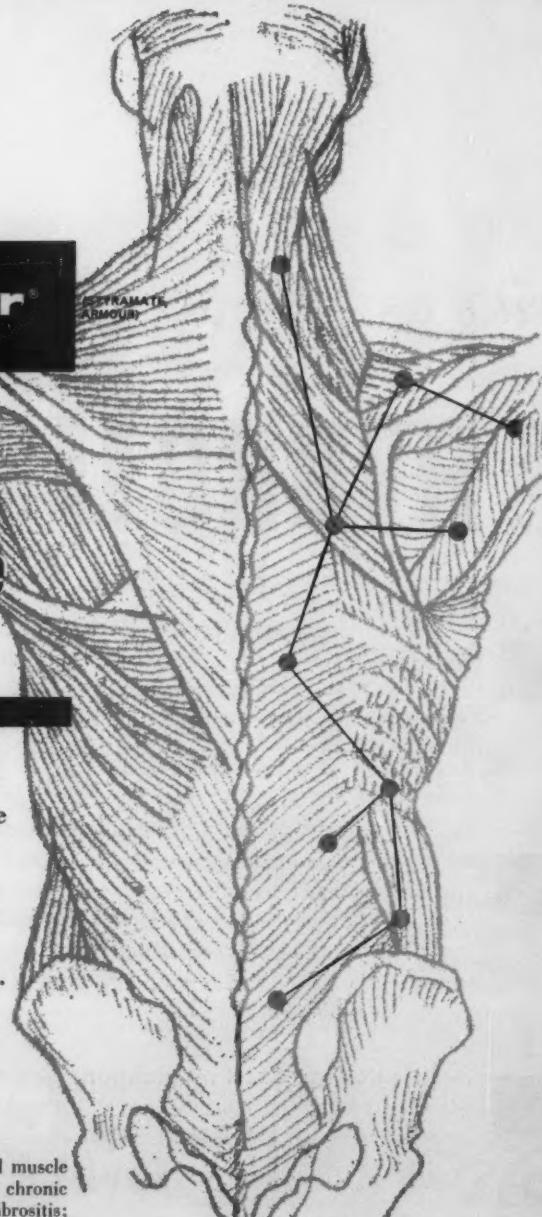
SUPPLIED: 200 mg. tablets in bottles of 50.

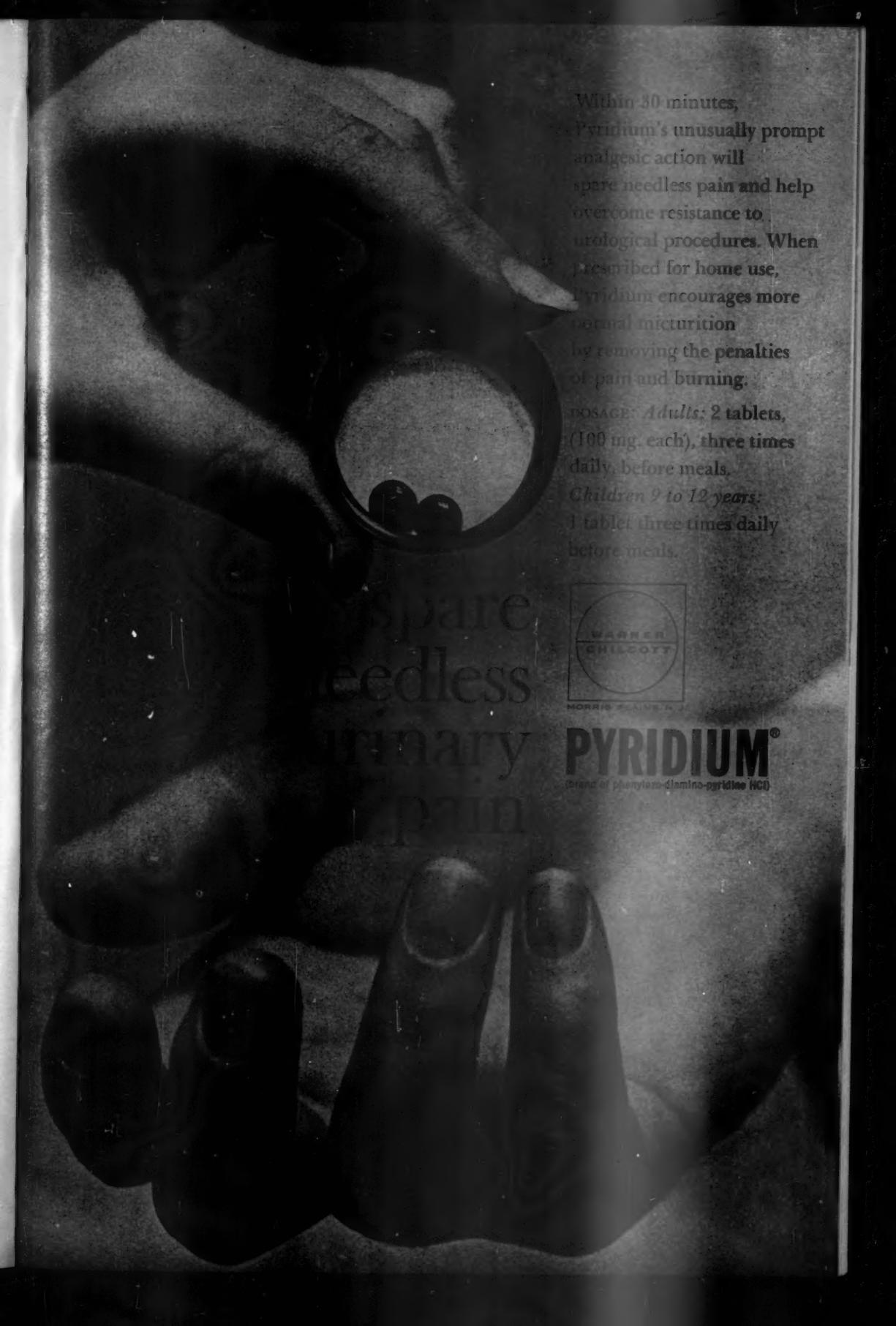
INDICATIONS: Any condition involving skeletal muscle spasm, as **musculoskeletal disorders:** acute and chronic back ache; arthritides; bursitis; disc syndrome; fibrositis; myalgia; myositis; osteoarthritis; following orthopedic procedures; rheumatoid arthritis; spondylitis; sprains and strains; torticollis; **neurologic disorders:** cerebral palsy; cerebrovascular accidents; cervical root syndrome; multiple sclerosis.

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Within 30 minutes,
Pyridium's unusually prompt
analgesic action will
spare needless pain and help
overcome resistance to
urological procedures. When
prescribed for home use,
Pyridium encourages more
normal micturition
by removing the penalties
of pain and burning.

DOSAGE: *Adults:* 2 tablets,
(100 mg. each), three times
daily, before meals.

Children 9 to 12 years:
1 tablet three times daily
before meals.



PYRIDIUM®

(Brand of phenylamino-dimino-pyridine HCl)

around the clock ulcer control with B.I.D. dosage

Just one 10 mg. Daricon tablet in the morning, and one at night before retiring, keeps your patient free from the pain and discomfort caused by gastrointestinal spasm, hypermotility, and hypersecretion.

Daricon is a remarkably potent and well tolerated antisecretory/antimotility agent. Its naturally prolonged action provides day and night relief of pain and symptoms associated with peptic ulcer, functional bowel syndrome, biliary tract dysfunctions, ulcerative colitis, and other gastrointestinal disorders characterized by spasm, hypermotility, and hypersecretion.

Dosage: 10 mg. b.i.d. (morning and evening).

**EVEN REFRACTORY
CASES RESPOND**

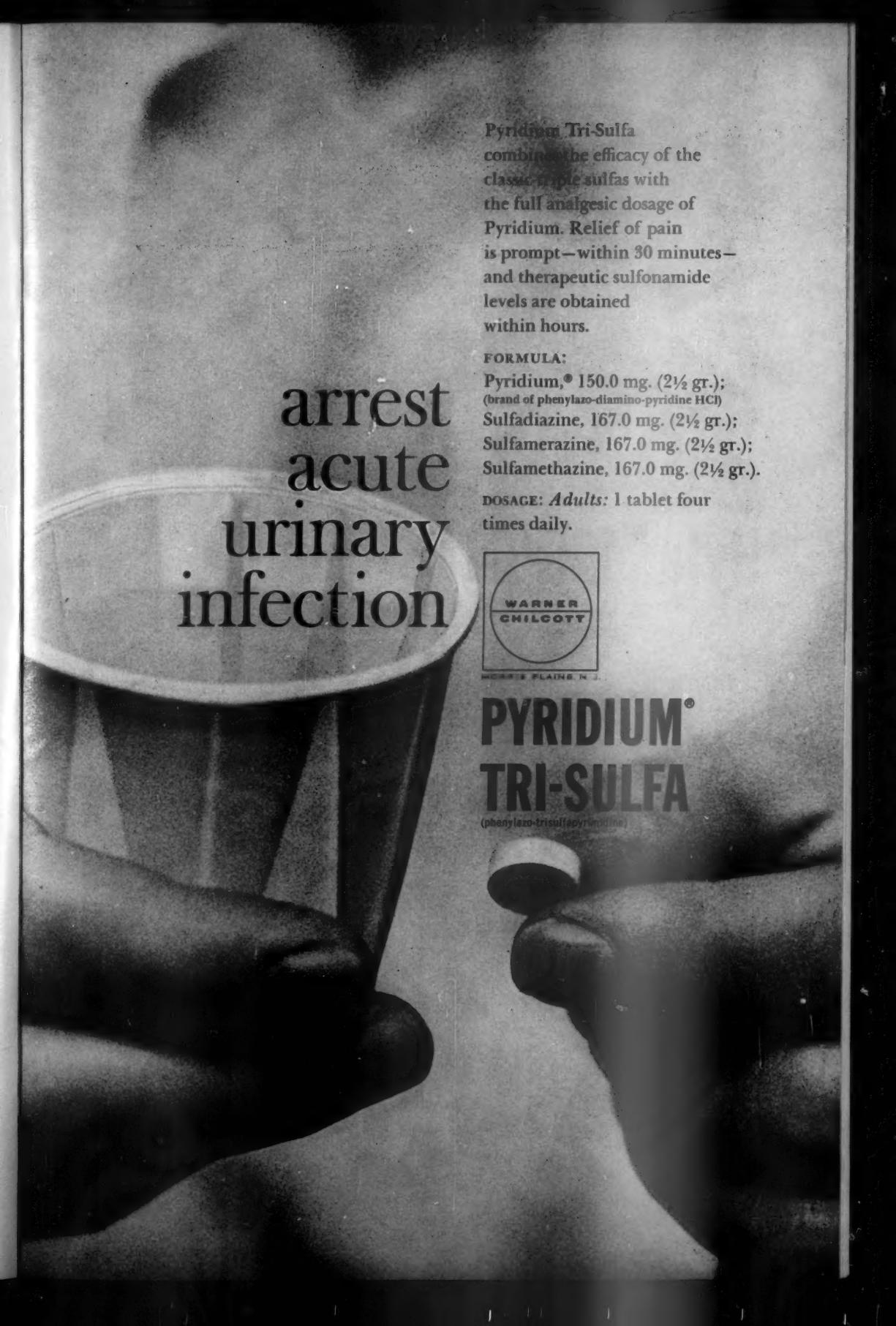
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DARICON

References: 1. Finkelstein, M., et al.: J. Pharmacol. & Exper. Therap. 125:330 (April) 1959. 2. McHardy, G., et al.: Postgrad. Med., in press. 3. Winkelstein, A.: Amer. J. Gastroenterol., in press. 4. Finkelstein, M., et al.: Presented at Fall Meeting, Amer. Soc. Pharmacol. & Exper. Therap., 1958. 5. Leming, B.: Clin. Med. 6:423 (March) 1959.

Trademark



arrest acute urinary infection

Pyridium Tri-Sulfa
combines the efficacy of the
classic-triple sulfa's with
the full analgesic dosage of
Pyridium. Relief of pain
is prompt—within 30 minutes—
and therapeutic sulfonamide
levels are obtained
within hours.

FORMULA:

Pyridium,® 150.0 mg. (2½ gr.);
(brand of phenylazo-diamino-pyridine HCl)
Sulfadiazine, 167.0 mg. (2½ gr.);
Sulfamerazine, 167.0 mg. (2½ gr.);
Sulfamethazine, 167.0 mg. (2½ gr.).

DOSAGE: *Adults:* 1 tablet four
times daily.



PYRIDIUM® TRI-SULFA

(phenylazo-trisulfapyridine)

NEW

rapid screening test for **AGAMMA-** **globulinemia**

and other abnormal levels of serum gamma globulin

Hyland GG-TEST*

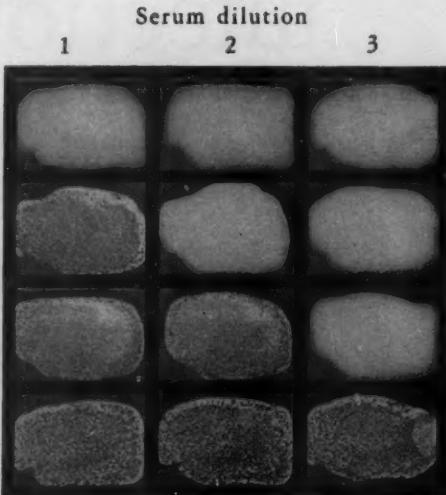
an accurate test for estimating
the 4 clinically significant
levels of serum gamma globulin

AGAMMA

HYPOGAMMA

NORMAL

HYPERGAMMA



*Trade Mark of Hyland Laboratories

Hyland GG-TEST requires only one drop of patient's serum and is performed simply and quickly on a glass slide (reactions in less than 2 minutes). Permits routine GG serum level determinations at low cost without overtaxing laboratory facilities.

Supplied: Kit containing Latex-Anti-Human Gamma Globulin Reagent and Glycine-Saline Buffer Diluent for 40 tests, Normal Serum Controls diluted ready for use, capillary pipettes for preparing serum dilutions, divided glass slide, and complete directions for the test. \$15.00 per kit.

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contro chronic urinary infection

Mandelamine's therapeutic distinction stems from its ability to control chronic urinary infections, including those resistant to antibiotics.

Mandelamine suits all age groups but it is particularly useful in older patients. Its antibacterial action is confined to the urinary tract; sensitization is unlikely; no fluids or alkalies are needed and cost is most economical.

DOSAGE: *Adults:* Average initial dosage is 1.0 to 1.5 Gm. four times daily.

Children over five:
0.5 Gm. four times daily.



MANDELAMINE®

(brand of methenamine mandelate)



STOP USELESS COUGH FOR 6,000 JET MILES

WITH A SINGLE DOSE OF

TUSSIONEX®

A 'Strasionic' Antitussive • Dihydrocodeinone Resin - Phenyltoloxamine Resin



2 oz.
TUSSIONEX®
liquid . . .
or 12
TUSSIONEX®
tablets . . .
a six day
supply

► ► ► as advanced as stratospheric jets. One shrinks
distance . . . the other stretches
time between coughs. Both spell progress.

8-12 Hour Cough Control with a Single Dose

Stop Useless Debilitating Cough without

impairing protection of cough mechanism

Adults:
1 tsp. or tablet q 12 h

Children:

Under 1 year.....½ teaspoon q 12 h
1-5 years.....½ teaspoon q 12 h
Over 5 years..... 1 teaspoon q 12 h

Each teaspoonful (5c.c.) or tablet Tussionex
provides 5 mg. dihydrocodeinone and 10 mg.
phenyltoloxamine as resin complexes

Rx only. Class B taxable narcotic.

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SUPPLY 90 AND 100 MG. TABLETS, BOTTLES OF 100, 1000 AND 5000.

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The look of 3 A.M.

"Send tetanus antitoxin!" The call had come from a Baltimore hospital. An accident victim. Jack Normile snapped the receiver in place. Minutes later, he and a Wyeth detail representative were at the refrigerator of the Wyeth Baltimore Warehouse, and the drug was on the way.

Emergency service like this is a matter of course to Jack Normile. One of the "night-people"? No, but it often seems so to physicians, pharmacists, and hospitals with a sudden need for a drug after hours. As Wyeth's Branch Warehouse Manager in Baltimore, Jack makes certain that he or one of his staff can be reached no matter what time it is.

Jack Normile has been in the thick of things almost from the day he joined Wyeth eighteen years ago in Chicago. Now serving thousands at professional and trade levels in Maryland and surrounding states, he assures the ready availability of products for medical practice. Whatever is needed, whenever and wherever it's needed, he sees to it that the drugs go out.

And all this is repeated in the fourteen other Wyeth Warehouses strategically situated throughout the country to serve the fifty states. Like Jack Normile and his staff, Wyeth Warehouse people everywhere are part of a network of service to physicians—a team prepared day in and day out for both the routine and the emergency needs of medical practice.

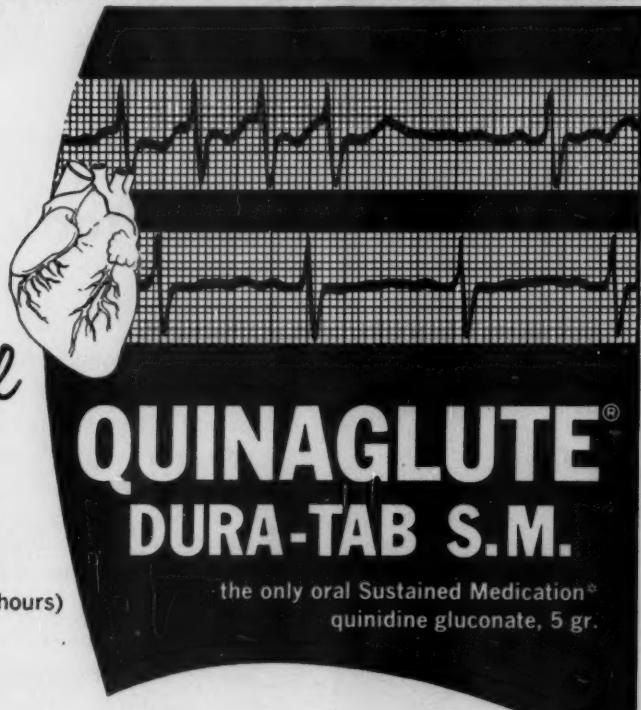


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quinidine
b.i.d.

(one dose every 12 hours)



for control of

cardiac arrhythmias

- each dose of Quinaglute Dura-Tab S.M.* maintains uniform plasma levels up to 12 hours.¹
- no night dosage needed.
- better absorbed and tolerated than quinidine sulfate.
- an unexcelled quinidine in premature contractions, auricular tachycardia, flutter, fibrillation.



Dosage: For conversion of auricular fibrillation to normal sinus rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days.

For maintenance 1 to 2 tablets every 10 to 12 hours.

Supplied: Bottles of 30, 100 and 250.

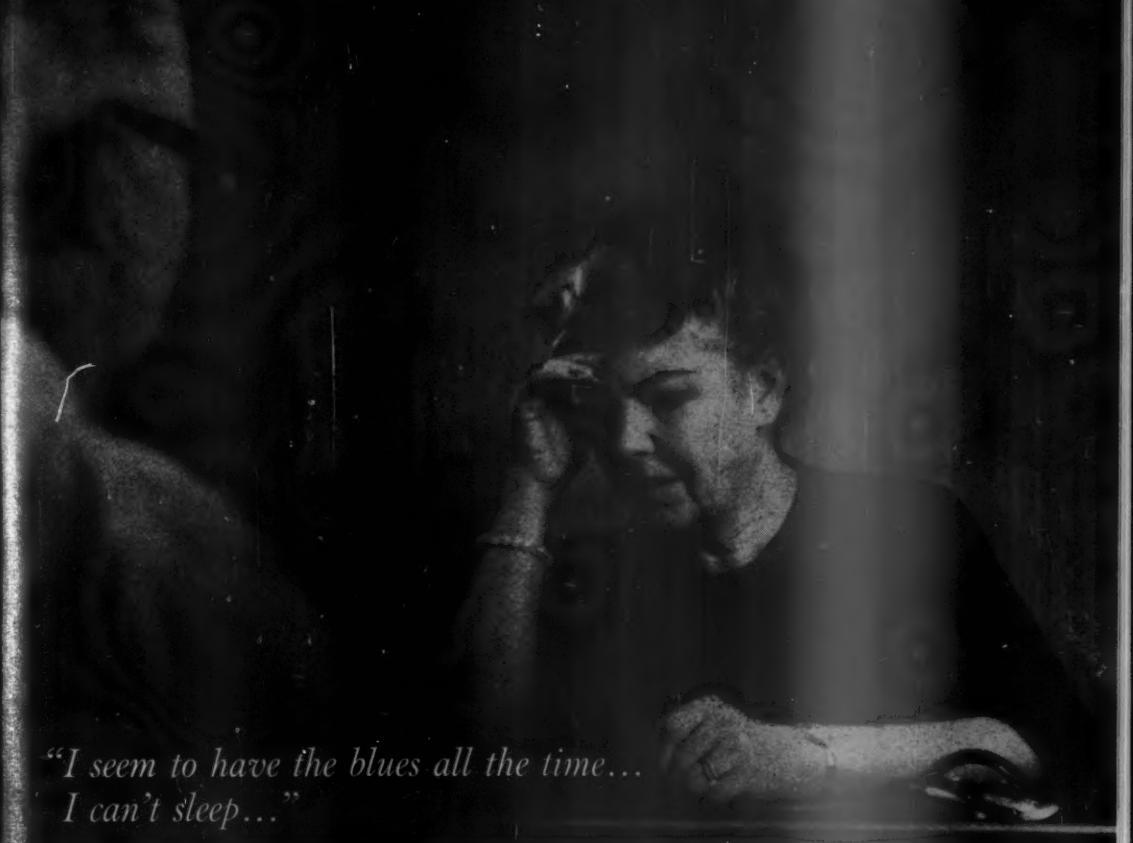
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CORPORATION
5119 West Stiles Street
Philadelphia 31, Pa.

1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

*Patent Applied For

Now also available... INJECTABLE QUINAGLUTE... 10 cc. Multiple Dose Vials, 0.08 Gm. Quinidine Gluconate per cc.



*"I seem to have the blues all the time...
I can't sleep..."*

in the depressed, unhappy patient
PROMPTLY IMPROVES MOOD
without excitation

- **Acts fast to relieve depression and its common symptoms:** sadness, crying, anorexia, listlessness, irritability, rumination, and insomnia.
- **Restores normal sleep**—without hang-over or depressive aftereffects. Usually eliminates need for sedative-hypnotics.

EFFICACY AND SAFETY CONFIRMED IN OVER 3,000 DOCUMENTED CASE HISTORIES.^{1,2,3}

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: Each light-pink, scored tablet contains 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

References:

1. Alexander, L.: J.A.M.A. **168**:1019, March 1, 1968.
2. Current personal communications; in the files of Wallace Laboratories.
3. Pennington, V.M.: Am. J. Psychiat. **115**:280, Sept. 1958.



for depression

Depron^{▲†}

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00-0150

IS THIS YOUR PATIENT?

1.

**EARLY POSTMENOPAUSE**

Complains of low back pain, vague aches and fatigue
Posture is poor
No x-ray evidence of bone lesions

2.

**LATER POSTMENOPAUSE**

Back pain is severe, spreading to hips ("girdle pain")
Patient is round shouldered, walks with a stoop
X-ray reveals compression fractures of lower vertebrae

3.

**70 AND OVER**

Fracture of hip after a minor fall
X-ray reveals fracture of neck of femur
X-ray reveals compression fractures of lower lumbar vertebrae

These three patients have osteoporosis. Early diagnosis and treatment with "Formatrix" is important because osteoporosis is probably the only age change that can be averted. With "Formatrix" therapy, relief from the symptoms of *low back pain, vague aches and fatigue* may be obtained in as little as a few weeks. "Formatrix" supplies the essential materials to stimulate increased bone formation and prevent further loss of bone substance that leads eventually to loss of height, stooped posture, and disabling fractures.

The highest incidence of osteoporosis may be found among the 14,000,000 women in the U.S.A. who are 55 years of age and over. Some investigators claim that almost all women past the menopause will show some degree of osteoporosis; furthermore, if all these women were examined carefully, 50 per cent would show x-ray evidence of decreased bone mass.

Suspicion may be the handiest diagnostic tool since presenting symptoms vary from mild to severe and incapacitating pain, and no x-ray evidence of spinal degeneration is available until about 30 per cent of the bone matrix is lost. Between these two extremes there are other signs of estrogen deficiency such as *wrinkled skin, a tendency to appear older than some years*; there may also be *hypercalciuria* when postmenopausal osteoporosis is complicated by acute osteoporosis of disuse.

Osteoporosis is primarily an atrophic condition of bone matrix formation and any factor that depresses osteoblastic activity or retards the formation of protein and connective tissue such as *prolonged immobilization, cortisone therapy, or malnutrition* will favor development of osteoporosis in both male and female.



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| Conjugated estrogens equine ("Premarin") | 1.25 mg. |
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Supplied: Tablets, bottles of 60 and 500.

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EARLY POSTMENOPAUSE

No x-ray evidence of bone lesion

2.



LATER POSTMENOPAUSE

X-ray reveals compression fracture of lower vertebrae

3.



70 AND OVER

X-ray reveals fracture of neck of femur

TO RELIEVE LOW BACK PAIN — TO PROMOTE HEALING OF FRACTURES

in osteoporosis

'FORMATRIX'

for matrix formation

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RG Lecithin, made wholly from soybeans, is an entirely wholesome food component and has been so used for more than a generation. There are no harmful side effects.³

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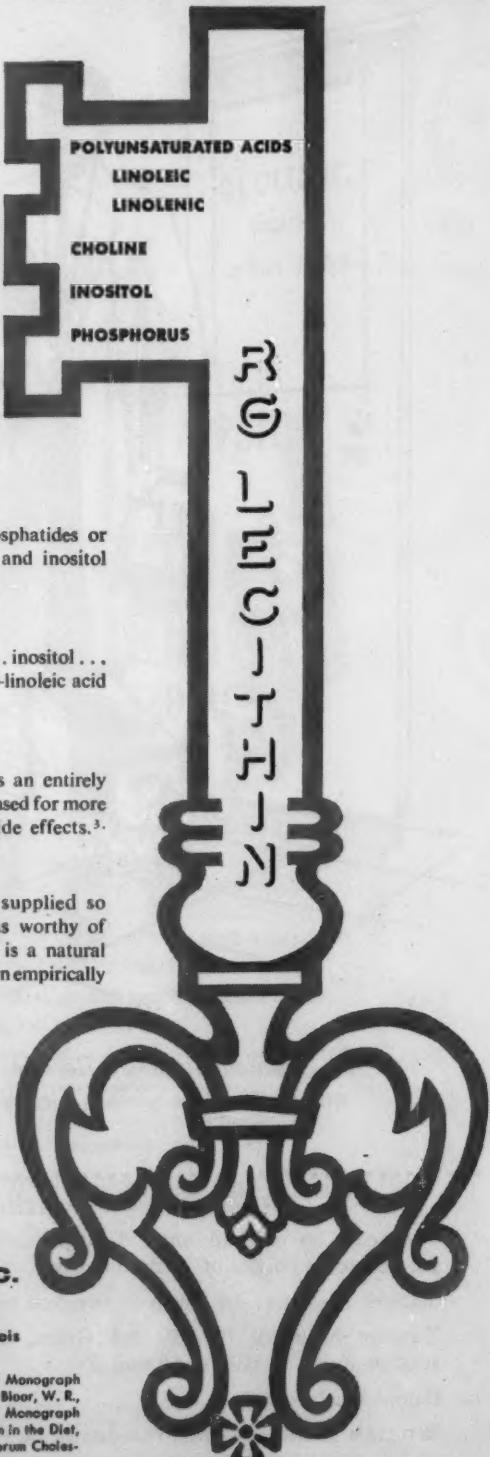
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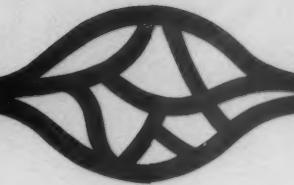
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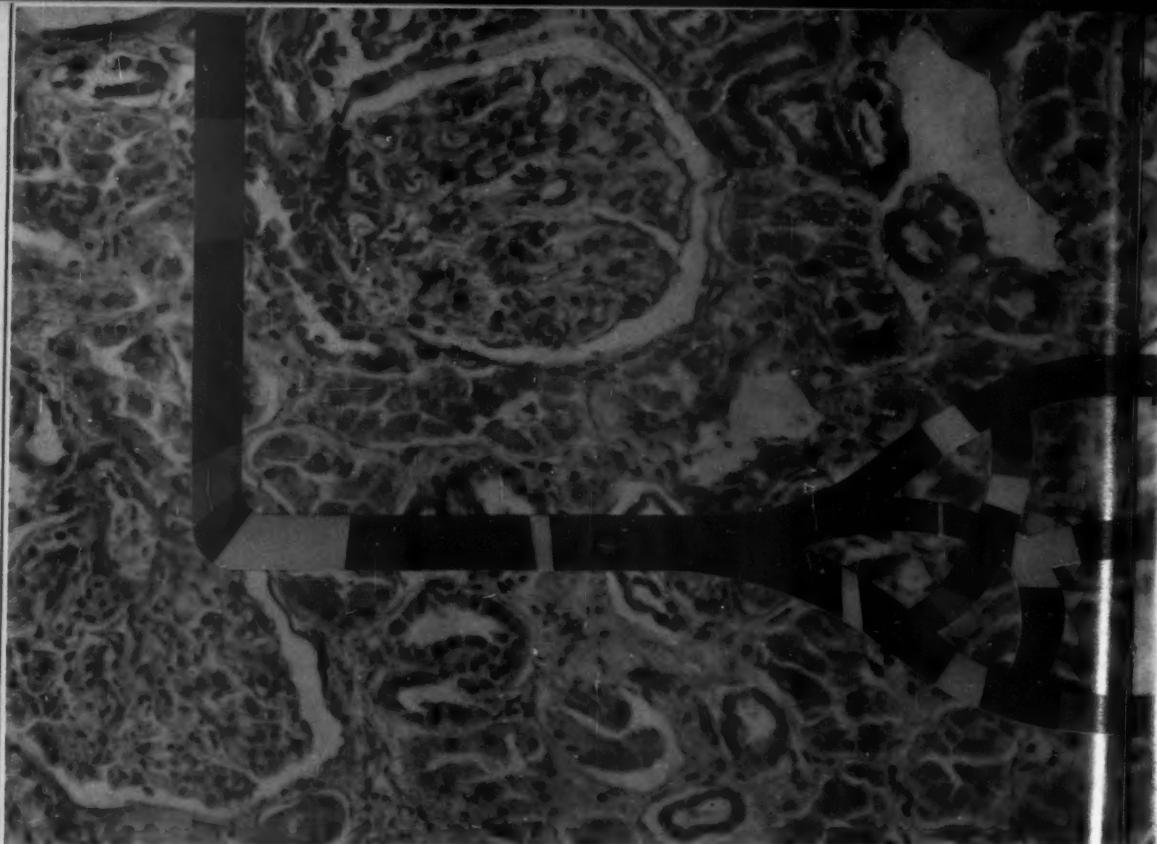
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Flumethiazide—the new, safe nonmercurial diuretic—rapidly achieves its diuretic effect without causing appreciable plasma electrolyte imbalance.^{1,2,3} Potassium loss is less than with other nonmercurial diuretics.¹ Moreover, the inclusion of supplemental potassium chloride in Rautrax provides added protection against



RAX

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Supply: Capsule-shaped tablets each providing 50 mg. Raudixin, 400 mg. flumethiazide, and 400 mg. potassium chloride, bottles of 100.

References: 1. Moyer, J.H., and others: Am. J. Cardiol., 3:113 (Jan.) 1959. • 2. Bodai, T., and others: To be published, Am. J. Cardiol., (April) 1959. • 3. Fuchs, M., and others: Monographs on Therapy, 4:43 (April) 1959. • 4. Montero, A.C.; Rochelle, J.B., III, and Ford, R.V.: To be published. • 5. Rochelle, J.B., III; Montero, A.C., and Ford, R.V.: To be published. • 6. Montero, A.C.; Rochelle, J.B., III, and Ford, R.V.: To be published. • 7. Doflerny, L.R.; Byrd, C.W., and Lilly, W.H.: North Carolina M.J. 70:430 (Oct.) 1958.

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1. Case reports on file, Wyeth Laboratories. 2. Parks, R.V., and Moessner, G.F.: Dual Approach to Patient Care, Scientific Exhibit, A.A.G.P., April, 1959.

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8. Straker, M.: Canad. M.A.J. 80:546, 1959.

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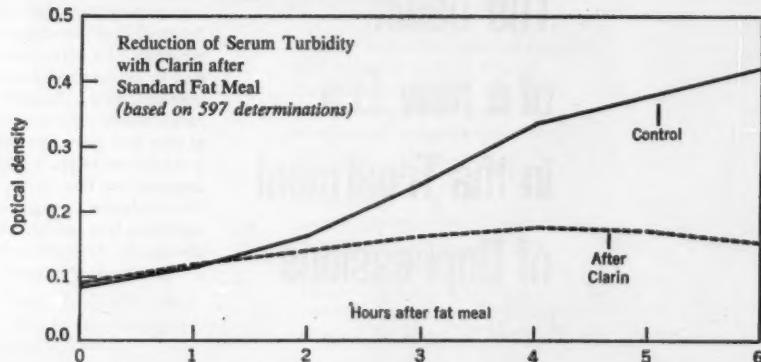
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1. Council on Drugs, J.A.M.A. 166:52 (Jan. 4) 1958.
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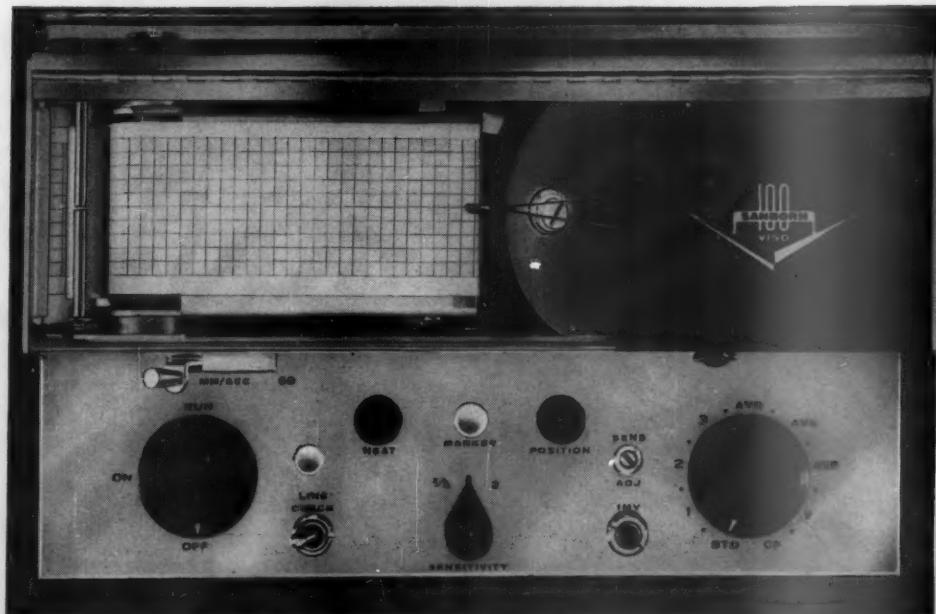




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References: 1. Reports on file, Roche Laboratories. 2. W. Schalck, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, in press. 3. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, 9:189, 1958. 4. W. B. Abrams, to be published. 5. O. Brandman, to be published. 6. Personal communications. 7. P. K. Conner, Jr., S. Kinard, W. Fraser, H. Bennett and J. H. Moyer, Scientific Exhibit, A.M.A. Clinical Meeting, Seattle, Nov. 27-30, 1956. 8. *New and Nonofficial Drugs*, Philadelphia. J. B. Lippincott Co., 1959, p. 362. 9. J. H. Moyer, in *Drugs of Choice 1958-1959*, St. Louis, The C. V. Mosby Co., 1958, p. 336.

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CUSHING'S SYNDROME: CLINICAL DIFFERENTIAL DIAGNOSIS AND COMPLICATIONS *

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IT is now accepted that the immediate cause of Cushing's syndrome is adrenocortical hyperfunction, regardless of the possible etiologic part played by the pituitary gland or the hypothalamus. The average duration of this syndrome from onset to death was estimated by Cushing¹ to be slightly over five years. The major causes of death are infection, complications of cardiovascular disease, and neoplastic disease.² The duration of the disease and its severity are considered to be important factors in treatment and prognosis.³ With a condition which is so potentially fatal, and in which the ravages of the disease are in part proportional to the length of time it is present, it becomes of utmost importance that a diagnosis be made at onset. Because great advances have been made in the laboratory evaluation^{4, 5} and management of these cases in recent years, and since complete remission can now be produced with a much higher degree of certainty than formerly, the importance of early recognition becomes even more apparent.

A series of 34 patients seen at the Lahey Clinic was recently reviewed.⁶ These cases were reevaluated with particular emphasis on early symptoms and the problems they may cause in differential diagnosis, in the hope that a better understanding of the onset of the disease and its earlier recognition would result.

CLINICAL MATERIAL

At the time the 34 patients (seven males and 27 females) came to the Clinic, the disease was in a more advanced stage than that which we are

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attempting to delineate in this study. In general, their diagnostic symptoms and signs conformed with the data published on similar groups of patients with Cushing's syndrome, and the incidence of each was as follows: fatigue, 79%; weakness, 71%; moon facies, 82%; buffalo hump, 71%; centripetal obesity, 59%; plethora, 73%; hirsutism, 93% of females; oligomenorrhea or amenorrhea, 92% of females; acne, 59%; bruises, 56%; striae, 56%; major mental changes, 18%; significant mental changes, 38%; minor psychologic changes, 32%; hypertension, 88%; duodenal ulceration, 9%; polycythemia, 52%; leukocytosis, 58%; relative lymphopenia, 83%; eosinopenia, 88% under 50 per cubic millimeter; decreased glucose tolerance, 88%; increased serum carbon dioxide, 38%; hypokalemia, 13%; decalcification of bones, 53%; pathologic fractures, 32%. Urinary 17-ketosteroids were elevated in 71% of the 28 cases in which this value was recorded. Variable and unreliable results were obtained in the determination of 11-oxysteroids. Of the 12 most recent cases, the urinary corticoids were elevated in 83% (method of Sulkowitch).

Surgical confirmation was obtained in 27 cases (adrenal carcinoma, one; adrenocortical adenoma, five; adrenocortical hyperplasia, 19; adrenal tissue aberrant in the pancreas, two). The remaining seven were diagnosed by the characteristic clinical signs and laboratory findings when first seen on an average of five years from the onset of the disease. In two patients the underlying pathologic factor remained unknown; in one of these, the results of retroperitoneal air studies were negative. Four responded to pituitary radiation, and in one of these, surgical exploration was performed to rule out the possibility of adrenal tumor; this was done before the time adrenalectomy was recommended for adrenocortical hyperplasia. In the seventh patient, the adrenals were found to be bilaterally enlarged at autopsy.

ONSET

Inquiries about the details of onset proved to be informative. It is commonly thought that the disease commences insidiously, and that a rapid beginning is indicative of an adrenocortical tumor. For purposes of review, a case was considered to be of rapid onset if the initial manifestations were dramatic enough to alert both the patient *and* the physician. It was found in this group of 34 cases (including all of the seven males) that 24 were of this type, five of such clear-cut, remittent character that the onset might be termed "episodic." The etiologic diagnosis in these 24 cases (71%) was: adrenocortical hyperplasia, 19 cases; adrenocortical tumor, three; carcinoma, one; adrenal tissue aberrant in the pancreas, one. Typifying these were eight cases in which the disease began with edema of the legs and face described as "swelling," "bloating" and "puffiness," accompanied by some other sign such as amenorrhea, renal colic, acne, hirsutism, bruises, weakness, mental symptoms or diabetes mellitus. Other patients complained of a sudden craving for food with increase in weight, one patient having an

increase of 40 pounds in one month. In two cases the initial symptom was renal colic with facial edema. The edema commenced one week before the renal colic in one, and two weeks after in the other. One of these patients had had three attacks of renal colic at yearly intervals. It was interesting to note that the onset in one was associated with symptomatic diabetes mellitus, and that a perforated duodenal ulcer was a landmark in a patient with episodic onset of symptoms, described below.

There were 10 cases (29%) with gradual onset, including two cases resulting from an adrenocortical adenoma, and one with adrenal tissue aberrant in the pancreas. The clinical manifestations began with mental changes, oligomenorrhea, gradual weight increase, hypertension, sterility, diabetes mellitus, and so forth, so that no definite date could be ascribed to their initial appearance. This group presented a different type of problem in differential diagnosis.

An outline of the initial symptoms of Cushing's disease would be incomplete without some reference to possible precipitating factors. Several patients described emotional strain before the onset of symptoms. In six patients, initial symptoms occurred following periods of unusual stress: a change of employment in one case, after marital separation in another, during a time when three jobs were held simultaneously in a third, when in solitary confinement after a prison riot in a fourth, working extra-long business hours in a fifth, and during a honeymoon in the sixth patient. The last patient was a 22 year old woman, who noted that her face began to swell while she was on her honeymoon. When she returned her friends commented on how fat she had become, although the scales recorded no increase. It was subsequently found that she had an aberrant adrenal tumor.

Another precipitating or aggravating factor in our series of cases was surgical or traumatic "stress," as illustrated by the following case of "episodic onset."

A 20 year old woman noticed increased facial hair following an appendectomy. She stated that this disappeared after hormone injections. At the age of 22 years, menstruation ceased after an accident. Menses returned to normal 11 months later, following another course of hormone injections. At the age of 25 years she had had an operation for a perforated duodenal ulcer, after which she noted a rapid gain in weight, increasing hirsutism, dyspnea and ankle edema. The only previous symptoms she mentioned were indigestion and epigastric pain for many years.

In view of this woman's history of gastrointestinal symptoms a number of possibilities arise, which will be discussed later. As far as she was concerned, her ill health and continuing symptoms had begun after her last operation.

DIFFERENTIAL DIAGNOSIS

The diagnostic problems generally fell into two groups, depending upon the type of onset. One third of our patients in whom the onset was rapid

had had edema of the face initially, and this was probably the greatest single cause of misdiagnosis before the patients came to the clinic.

In seven patients, hypothyroidism was diagnosed or suspected at some time. This diagnosis was made when facial bloating was accompanied by fatigue, mild cold intolerance and, in some, a dry skin and slow pulse. At this early stage of the disease the facial puffiness may not be accompanied by the usual plethora, but the patients may even exhibit a degree of pallor. Suspicions in these cases were often "confirmed" by finding a low basal metabolic rate or high blood level of cholesterol. Therapeutic administration of thyroid was ineffective in all cases, and sometimes intensified the irritability so often present in this disease.

On the other hand, three of the patients were previously considered to have hyperthyroidism because of the appearance of increased nervousness, irritability, sweating and increased basal metabolic rate. In one patient, subsequent subtotal thyroidectomy elsewhere was followed by mental sluggishness. Another was given radioiodine therapeutically, without effect at the time of her admission for adrenalectomy.

A search for the additional signs of Cushing's disease, some of which are always present, combined with the fact that the basal metabolic rate and blood cholesterol give contradictory information, should be sufficient to alert the physician to the possible presence of Cushing's disease. Individual determinations of cholesterol, basal metabolic rate or radioiodine uptake may be normal, high or low.^{2, 6, 7}

It should be mentioned here that, although the skin in patients with Cushing's syndrome is classically thin and may be somewhat oily, in five cases observers noted it to be dry and coarse and, in one, thickened. This was a contributory factor in the misdiagnosis, and possibly resulted from the presence of unrecognized diffuse edema. The thinning of the skin, which inevitably occurs, may not be present in early cases, and must usually be in the mind of the observer before it is recognized, unless obvious violaceous striae indicate it. The most recent patient noted to have a dry skin stated that since her illness had begun she no longer needed to use her many hand creams. Five patients noted increased sweating, in two of whom it was profuse.

Another diagnostic pitfall was to consider the facial swelling to be of renal origin, especially if it was worse in the morning. A diagnosis of nephritis or nephrosis was considered in three of our group. Wolff⁸ reported a case of swelling of the face, abdomen and lower limbs of two months' duration. A diagnosis of Type II nephritis (Ellis' classification) was made when an elevated blood cholesterol and a low total protein were found. Autopsy one month later revealed an adrenocortical carcinoma, and macroscopically and microscopically normal kidneys.

Facial edema, which developed in one case following renal colic, was

considered to be an allergic reaction to the dye used for pyelography. In two cases, food allergies were suspected. Because of pronounced muscle weakness coexistent with a "thick" skin, another patient was thought to have dermatomyositis. Three patients had full liver, cardiac and renal studies which failed to reveal the cause of the edema.

Much mention has been made of edema, bloating and swelling. These symptoms need further discussion because they have not, to our knowledge, been emphasized in any of the published reports of Cushing's syndrome. The incidence of edema, without comment on its distribution, was reported to be 60% in one series.⁹ In the subsequent discussion, one of the authors mentions a patient with the presenting symptom of edema. This disappeared after adrenal surgery, and reappeared with the recurrence of increased steroid output. Approximately 20% of another group had edema of the ankles and hands.⁷ In our 34 cases, edema or a history of edema of the ankles was present in 17 (due to congestive heart failure in three), and of the face in 14. When edema is due to cardiac decompensation resulting from the hypertensive and vascular changes so common in Cushing's syndrome, the cause can readily be ascertained. There may be some sodium retention resulting from excess production of hormones with aldosterone-like effect, and one might possibly expect some resultant dependent edema. However, an explanation of the facial edema is required. Redistribution of the fatty depots, due to the effects of excess gluco-corticoids on fat metabolism, will result in rounding of the cheeks (moon face), and the patient may complain of a swollen face or a "tightness" of the facial skin. However, in some of the cases to which we have referred, the appearance of facial swelling was dramatic enough to suggest the known common causes of facial edema: nephritis, nephrosis, hypoproteinemia and allergy. Fluctuation of this sign in some of the cases, its accentuation in the morning and before menstrual flow in one case, and involvement of the periorbital tissues in five of our cases (with a history of this in two others), all point to an edematous origin. In the two cases where they were tried, there was a marked response to diuretics.

A possible explanation for the facial edema is the tendency to low total protein values which, in one of our patients, was below the "critical level"¹⁰ for the development of edema. It has been demonstrated that patients with Cushing's syndrome, and those receiving cortisone therapy, exhibit hypoalbuminemia.¹¹ In seven of the 14 of our cases where this was recorded, the total protein value was below 6.5 gm. per 100 c.c. The average level of serum albumin in 13 cases was 3.71 gm. per 100 c.c. However, many of the estimations in our cases were not carried out when the edema was present, so that no direct correlation could be made. In the cited case simulating Type II nephritis,⁸ the total protein value was 4.6 gm. per 100 c.c., which is also below the aforementioned critical level. It may be stated,

then, that the probable cause for the edema is a combination of factors, including the tendency to hypernatremia, hypoproteinemia and vascular fragility, all of which occur to varying degrees in Cushing's syndrome.

Finally, the problem of mental change was often encountered. Some irritability or emotional change occurred in 88% of our patients. This may mislead the physician and cause him to think that the condition is one of psychosomatic origin. Major mental changes were seen in six patients, however, with a suicidal tendency in three. One patient with facial swelling had an acute schizophrenic reaction at onset. Thirteen patients showed significant mental symptoms. Two patients had previously had electroconvulsive therapy. Hence, if the association is not kept in mind, these changes may constitute a real stumbling block in the diagnosis of Cushing's disease.

The second group is made up of the cases with gradual onset of symptoms, which often constitute a more difficult diagnostic problem. Patients in whom a history of rapid onset had not been elicited are usually included in this group. The importance of taking accurate histories is borne out by the fact that in 71% of cases the onset was rapid, and that this type of onset, if recognized, will lead to an earlier diagnosis. When the disease commences insidiously, a list of the individual manifestations of Cushing's syndrome which are also attributable to some other diseases must be considered in the differential diagnosis. With this type of onset the disease often remains unrecognized for long periods of time, until the classic picture finally develops. Among the more common findings are obesity, hypertension, hirsutism, diabetes mellitus, amenorrhea and mental changes. There are many helpful pointers to the diagnosis, such as the combined appearance of signs, high hemoglobin and leukocytosis with relative lymphopenia (under 15% of total count in 42% of our cases) and eosinopenia (78% below 50 per cubic millimeter), the very high incidence of fatigue and weakness, together with nervous complaints and the striking change in appearance. Comparison with a previous photograph may be helpful if the "moon face" is in doubt. The centripetal obesity is obvious if the limbs are strikingly thinner, as is frequently the case. The complexion is usually florid, sometimes causing patients to look healthiest when they feel the worst. The classic differential problem of the obese woman with mild hirsutism, diabetes, hypertension and possibly postmenopausal amenorrhea and osteoporosis should present no such problem if the onset of symptoms is considered, change in physical appearance is assessed, and the other indices are examined. An awareness of the possibility of Cushing's disease in these cases is the safeguard against missing the diagnosis. Determination of the 17-hydroxycorticosteroid output in several 24-hour specimens of urine alone, or after ACTH stimulation, should help to establish the diagnosis in the majority of such cases.

Less common problems in differentiation at initial presentation are diabetes mellitus or complications of peptic ulcer. The occurrence of diabetes

mellitus as the only endocrine abnormality must be extremely rare.¹² Hematologic investigations were made in some cases when polycythemia or the hemorrhagic signs (bruising, ecchymosis, and so forth) so common in Cushing's disease were present. Hyperparathyroidism was suggested by the radiologist as a diagnosis in several cases of osteoporosis and renal calculi. Minimal elevation of the serum calcium and a tendency to low serum phosphorus may be causes for concern in these patients. Minute renal cortical calcification was present in one case. Needless surgery for "hyperparathyroidism" in a case of Cushing's syndrome has been reported.¹³ However, renal calculi in the absence of biochemical changes or osteoporosis may be considered "idiopathic"; these conditions existed in our two patients who had renal colic as their presenting symptoms. The high incidence of renal calculi⁶ and colic in cases of Cushing's syndrome emphasizes the importance

TABLE 1
Common Initial Signs and Differential Diagnoses in Cushing's Disease

| <i>Common Initial Signs</i> | | <i>Rapid Onset</i> | <i>Differential Diagnoses</i> |
|---|--|--|-------------------------------|
| Facial edema | | Hypothyroidism | |
| Rapid weight gain | | Nephritis or nephrosis | |
| Renal colic | | Allergic or cardiac edema | |
| Amenorrhea with facial edema or rapid weight gain | | Simple obesity | |
| Physical weakness | | Idiopathic renal calculi | |
| Mental disturbance | | Psychoses | |
| | | Collagen disease | |
| <i>Common Presenting Signs</i> | | <i>Gradual Onset</i> | <i>Differential Diagnoses</i> |
| Gradual weight gain | | Simple obesity | |
| Oligomenorrhea and hirsutism | | Familial hirsutism; psychogenic amenorrhea | |
| Diabetes mellitus | | Diabetes mellitus | |
| Hypertension | | Essential hypertension | |
| Mental or emotional changes | | Psychosomatic conditions | |
| Osteoporosis | | Postmenopausal osteoporosis | |

Other differential diagnoses: hyperthyroidism, Guillain-Barré syndrome or diabetic neuropathy, hyperparathyroidism, peptic ulcer, polycythemia, purpuras, ovarian tumors.

of this differential. Two patients had major complaints referable to pathologic fractures; however, this was in a later stage of the disease.

The textbook inclusion of hypertension on the list of differential problems still needs repetition. As late as 1952, one of our patients had a thoracolumbar sympathectomy elsewhere for "essential hypertension." Mixed syndromes (or the adrenogenital syndrome) are not of such great importance in clinical differential diagnosis, because in such instances attention is necessarily directed to the adrenal glands.

Table 1 lists the more common initial signs in our two arbitrarily defined groups of patients. The accompanying listing of differential diagnoses indicates the frequency with which they arise in each group, but there is a certain amount of overlap in this regard.

SUMMARIES OF TYPICAL CASES

I. Cases of Rapid Clinical Onset

Case 1. A 33 year old white man had had sudden, recurrent facial and periorbital swelling associated with slight ankle swelling six months before admission to the clinic. He had also noticed an acneiform eruption. Progressively increasing weakness of the legs resulted in difficulty in climbing stairs. Three months later he had a hemorrhage from a duodenal ulcer without previous gastrointestinal symptoms. Impressions originally were that he had nephritis or some collagen disease.

The patient's major complaint on presentation was muscle weakness. He had a typical cushingoid appearance, including a "moon" face, acne, plethora, a buffalo hump and limb-sparing obesity (despite a weight loss over the period of symptoms). The blood pressure was 160/106 mm. of Hg and he had a diabetic glucose tolerance curve. The results of hematologic studies were as follows: sodium, 141 mEq. per liter; potassium, 3.7 mEq. per liter; calcium, 9.6 mg. per 100 c.c.; cholesterol, 212 mg. per 100 c.c.; hemoglobin, 16.0 gm.; red cells, 4,800,000; white cells, 12,800, with 22% lymphocytes; total eosinophils, 32; sedimentation rate, 6. The findings on skull x-rays were negative, and a 24-hour urine specimen showed 35.7 mg. 17-ketosteroids and 0.28 mg. 11-oxysteroids. Subsequent subtotal adrenalectomy revealed adrenal hyperplasia.

Case 2. A 35 year old white woman had noted facial swelling with puffiness of the eyelids and legs for one month. Food allergy was first considered. From that time she noticed increased growth of facial hair and some mental symptoms. On admission the skin was dry, the pulse rate was 52, and the face was somewhat pale. First suggestions on appearance were myxedema, or nephrotic syndrome.

The patient was extremely nervous, and within the next few days hallucinations developed and she exhibited an acute schizophrenic reaction. On examination her face was rounded, with puffiness of the eyelids, hirsuties, and 2 plus ankle edema. No plethora, striae, bruising or acne was present. Weight was unchanged. The menstrual periods were normal, but libido was reduced. Blood pressure was 145/85 mm. of Hg. The results of blood studies were: sodium, 149 mEq. per liter; potassium, 3.6 mEq. per liter; chloride, 93 mEq. per liter; carbon dioxide, 36 mEq. per liter; hemoglobin, 12.8 gm.; red cells, 4,340,000; white cells, 11,750, with 10.5% lymphocytes; total eosinophils, 19; basal metabolic rate, plus 15; cholesterol, 120 mg. per 100 c.c.; protein-bound iodine, 3.0 μ g. per 100 c.c. There was a diabetic glucose tolerance curve. Twenty-four-hour urine specimen showed 47 mg. 17-ketosteroids and 48 mg. corticoids (Sulkowitch's assay). Roentgenograms of the skull revealed no abnormality except for frontal endostosis; no osteoporosis was present. The adrenal specimen after total adrenalectomy revealed adenomatous hyperplasia.

Case 3. A 34 year old white man had renal colic, followed in one week by swelling of the face, hands, wrists and knees. Allergy to the dye given for intravenous pyelogram was considered. Renal colic without swelling recurred a year later. One year later he had a third attack of renal colic, after which he continued to have intermittent bloating of the face, abdomen and thighs. He stated that it varied in severity. During the year he had thorough cardiac, liver and renal investigations, but a diagnosis was not made.

On examination at the Clinic the patient had a typical cushingoid appearance, including the "moon" face, buffalo hump, limb-sparing obesity, acne and plethora. Blood pressure was 155/105 mm. of Hg. The results of blood studies were: serum sodium, 150 mEq. per liter; carbon dioxide, 28.6 mEq. per liter; calcium, 10.2 mg. to 11.4 mg. per 100 c.c.; phosphorus, 2.8 mg. per 100 c.c.; hemoglobin, 14.6 gm.; red

blood cells, 4,600,000; white blood cells, 6,950, with 37% lymphocytes (later, 15% lymphocytes); total eosinophils, 31; erythrocyte sedimentation rate, 12; cholesterol, 174 mg. to 257 mg. per 100 c.c. There was a diabetic glucose tolerance curve. Twenty-four-hour urinary 17-ketosteroid value was 11.7 mg. Roentgenologic studies revealed a renal calculus on the right. On a perirenal pneumogram, a right adrenal enlargement was questionable. The minor mental changes became more pronounced during a course of pituitary irradiation, so subtotal adrenalectomy was performed; this revealed adrenal hyperplasia.

Case 4. A 25 year old white man had changed his job a year before admission to the Clinic. At about the same time he noted a sudden craving for sweets, and gained approximately 40 pounds in one month. He became emotionally upset, exhausted and sleepy. He lost 26 pounds on a reduction diet. Nine months later he noted facial puffiness, at which time he complained of cold intolerance and mental sluggishness. When a low basal metabolic rate was found he was given thyroid, without benefit.

On admission to the Clinic the patient's chief complaints were nervousness, exhaustion, cold intolerance and weight fluctuation. He presented the typical cushingoid configuration, including a "moon" face, buffalo hump with kyphosis, and thinning of the limbs. He was plethoric, and had purplish striae in the axillae, buttocks, groin and thighs. Blood pressure was 120/80 mm. of Hg. Blood studies gave the following results: sodium, 145 mEq. per liter; potassium, 3.3 mEq. per liter; calcium, 10.1 mg. per 100 c.c.; phosphorus, 3.8 mg. per 100 c.c.; hemoglobin, 15.2 gm.; non-protein nitrogen, 47 mg. per 100 c.c.; proteins, 6.9 gm. per 100 c.c.; blood sugar (one hour after glucose), 177 mg. per 100 c.c.; basal metabolic rate, minus 17; cholesterol, 163 to 182 mg. per 100 c.c. Roentgenograms showed pronounced osteoporosis and bilateral renal calculi. Operation revealed a right adrenal adenoma.

Case 5. A 20 year old white clerk, while in prison for petty forgery, was sentenced to solitary confinement following a prison riot. On a diet of bread and water he commenced to gain weight rapidly (30 pounds by time of discharge). At the same time he felt bloated and thirsty, and perspired profusely. Subsequently he noted falling of head hair, loss of libido and irritability. Thyroid surgery was followed by mental and physical sluggishness.

The patient was subsequently seen by Dr. Cushing, who referred him to the Clinic for hypophysectomy. He had the classic signs of cushingoid configuration, plethora, acne, purple striae, hypertension and osteoporosis with pathologic fractures. He died one week after operation. At autopsy the right adrenal gland weighed 12 gm. and the left, 10 gm. Dr. Cushing's staff examined the pituitary and noted Crooke's changes.

Case 6. Three years before admission, a 28 year old white housewife noticed swelling of the face, hands and feet of relatively sudden appearance. This became worse in the mornings and before menstrual periods. One year later she first noticed marked emotional upsets. A thoracolumbar sympathectomy for "essential hypertension" was performed a year before admission.

On admission to the Clinic the patient complained of emotional upsets, and the typical cushingoid configuration was noted. Plethora, acne, minimal bruising, hirsuties and amenorrhea were described. Blood pressure was 195/105 mm. of Hg. The results of blood studies were: hemoglobin, 14.6 gm.; red blood cells, 4,990,000 and 5,300,000; white blood cells, 12,900, with 37% lymphocytes; total eosinophils, 12; blood sugar (one hour postprandially), 416 mg. per 100 c.c. Corticoids in a 24-hour urine specimen were 14.3 mg. (Sulkowitch's assay). On the basis of the history and the findings, including the elevated urinary corticoids, surgery was advised but the patient initially refused. Three years later a right adrenocortical adenoma was removed.

II. CASES OF GRADUAL CLINICAL ONSET

Case A. A 30 year old white school teacher had noted a gradual weight gain for five or six years. She also complained of lassitude, headaches and amenorrhea. Increasing hypertension was noted. A diagnosis of malignant hypertension was made.

The classic picture of Cushing's syndrome had developed by the time the patient came to the Clinic. She had a cushingoid configuration, with a buffalo hump and limb-sparing obesity. Plethora, bruising, striae, hirsuties and amenorrhea were present. Blood pressure was 220/160 mm. of Hg, with grade IV hypertensive retinopathy. The results of blood studies were as follows: red blood cells, 5,500,000; white blood cells, 12,650; hemoglobin, 103%; cholesterol, 275 to 380 mg. per 100 c.c. There was a diabetic glucose tolerance curve. Roentgenograms of the skull showed a normal sella turcica. At operation the left adrenal containing an adrenocortical adenoma was removed.

Case B. A 36 year old white housewife had noted irritability and decreased capacity for concentration and memory for two years. Depression was marked (twice she had attempted suicide). Listlessness, cold intolerance and amenorrhea were described. Therapeutic thyroid administration one year previously had been without benefit. At the Clinic the patient was seen to have a cushingoid configuration, with hirsutism, amenorrhea, hypertension, a diabetic glucose tolerance curve and a characteristic blood picture. Subtotal adrenalectomy did not produce a remission. Subsequent operation, when a 14-gm. aberrant adrenal gland was removed from the body of the pancreas, produced successful results.

Case C. A 42 year old white housewife had had high blood pressure for seven or eight years before admission. She had had a "nervous breakdown" three or four years later, for which shock therapy was given. When she was 15 years of age, subtotal thyroidectomy was performed for thyrotoxicosis. Radioactive iodine uptake was slightly elevated six months before admission. She was given radioiodine therapy.

The classic picture of Cushing's disease was noted on admission. The patient also had plethora, bruises, hirsuties and oligomenorrhea. Blood pressure was 206/138 mm. of Hg, with grade II hypertensive retinopathy. The results of blood studies were as follows: hemoglobin, 16.4 gm.; red blood cells, 5,350,000; white blood cells, 15,400, with 6.5% lymphocytes; total eosinophils, 7; proteins, 6.4 gm. per 100 c.c.; nonprotein nitrogen, 31; cholesterol, 291 mg. per 100 c.c. A one-hour, two-dose glucose tolerance test gave positive results. Roentgenograms showed generalized decalcification, with a healed fracture of the pubic ramus. Areas of radiolucency were noted also in the skull films. A 24-hour specimen of urine contained 18.3 mg. 17-ketosteroids and 48.8 mg. total corticoids (Sulkowitch's assay). The presence of adrenal hyperplasia was confirmed at operation.

Case D. A 43 year old white housewife had had a miscarriage two years before admission, followed by oligomenorrhea, nervousness, a craving for foods and weight increase (20 pounds in two years). She also complained of fatigue, excessive perspiration and ankle swelling.

On presentation the patient had a cushingoid configuration with plethora. The findings of hypertension, a diabetic glucose tolerance curve and osteoporosis were further confirmation of this diagnosis. A 24-hour specimen of urine contained 2.9 mg. 17-ketosteroids and 15.2 mg. corticoids (Sulkowitch's assay). An adrenocortical adenoma was removed at operation.

COMPLICATIONS

In a disease with such protean manifestations, it is sometimes difficult to know which should be considered to be complications. For example, the probable negative protein and calcium balances may cause osteoporosis

(53% of our cases) as a sign; however, pathologic fractures (32% of cases) and renal calculi (30% of cases) could be viewed as complications of the disease. Moreover, one of our cases showed multiple renal cortical calcifications. Of interest in this connection is the report¹⁴ that in 11 of 17 autopsied cases of Cushing's syndrome, calcium deposits were present in the renal tubules.

Hypertension (present in 88% of our cases) is another common sign of Cushing's syndrome; however, there is always the danger that it will become a complication. Sprague et al.¹⁵ have reported that, of 44 cases with hypertension before surgery, 16 continued to have high blood pressure in remission. The prominence of other cardiovascular complications is now well known.^{2, 13} Of this group, three patients had cerebrovascular accidents. One of them had had hypertensive left ventricular failure on a previous occasion. One patient died of acute pulmonary edema, while another had a coronary thrombosis and left ventricular failure, and subsequently thrombosis of the right femoral artery developed.

The susceptibility of patients with Cushing's syndrome to infections has probably been the most often discussed complication in previous years. In this series, infection was severe enough to cause death in three cases, one of which occurred recently from a staphylococcus resistant to antibiotics. Infections have been the greatest single cause of death in the past, and, despite antibiotics, they are still a big problem. This is borne out by the fact that they continue to complicate cortisone therapy.¹⁶

Three patients (9%) had duodenal ulcers, one with perforation at onset, and the other two accompanied by melena. The patient with perforated ulcer (described earlier) had had gastrointestinal symptoms for many years. She considered the operation to be the landmark of the onset of her symptoms. It is quite possible that the onset of the disease caused reactivation of a previous ulcer, resulting in perforation. However, she had had two previous episodes indicating possible temporary adrenal overactivity. Mild unrecognized hyperfunction may have been responsible for the previous ulcer symptoms. The stress of an operation may have brought a "symptomless" increased level of cortical secretion up to a level sufficient to cause the more obvious picture. The cause of ulceration is presumably associated with the increase in secretion of gastric acid and pepsin resulting from adrenocortical hormone action. The incidence of peptic ulceration in these cases is within the cited range of 5 to 10% for the normal population. Similarly, the incidence of ulceration with the use of therapeutic steroids may be within the "natural" range. However, Kirsner,¹⁷ in an excellent review, concluded that the association between steroids and peptic ulceration appeared to be significant.

Three of our patients developed symptoms and signs of multiple peripheral neuritis, considered to be typical of the Guillain-Barré syndrome.^{18, 19} Two of these were the first cases to be recorded with this complication.¹⁸ Since then, two other cases have been reported.^{20, 21} This is of particular interest

in view of the many favorable reports on the treatment of this syndrome with ACTH and cortisone.

The spinal fluid protein in the five reported cases ranged from 30 mg. to 115 mg. per 100 c.c., and was normal in only one instance. However, the classic albumocytologic dissociation may not necessarily be present; in fact, both normal cerebrospinal fluid protein and pleocytosis have been reported in cases of the Guillain-Barré syndrome.²² In addition, in four of five other cases of Cushing's syndrome where the spinal fluid protein was determined, it was elevated (total range, 39 mg. per 100 c.c. to 125 mg. per 100 c.c.). In this connection it should be mentioned that, in Joslin's control group of diabetics, the cerebrospinal fluid protein was elevated in 26%.²³ In all these cases of Cushing's syndrome there was either frank diabetes or evidence of abnormal carbohydrate metabolism. In view of this, no definite deductions can be made at present from this sign.

Many questions could be raised with regard to this neurologic complication of Cushing's syndrome. The incidence of cranial nerve involvement is very high in the Guillain-Barré syndrome,^{22, 24} but this was not present in any of the cases of Cushing's disease with neuropathy. Again, sphincter involvement is early and transient²⁴ in the Guillain-Barré syndrome, and it was late and severe in one of our three cases. Diabetic neuropathy, which may be indistinguishable from the Guillain-Barré syndrome, usually appears in patients with diabetes of long standing, but may precede the onset of diabetes.²⁵ The relation of Cushing's neuropathy to the presence of diabetes, then, needs further study.

We have no explanation as to why this condition has not been previously reported. Too many of the signs may have been attributed to the muscle weakness resulting from protein loss, or loss of reflexes and weakness due to the hypokalemia. That these factors are, at most, only contributory may be inferred from the fact that the serum potassium level was normal in one case, that the neuropathy was not affected by the administration of potassium before surgery in another, and that it continued after adrenalectomy in at least two instances. The report as far back as 1934 of a patient who had swelling of the hands, feet and face and who developed weakness with a steppage gait²⁶ makes us wonder whether we are not just now beginning to recognize the more serious instances of this complication, and have been overlooking the mild ones. The presence or absence of sensory changes in this case, however, was not reported.

In general, the etiologic mechanisms of peripheral neuritis are not well understood. In particular, should Cushing's neuropathy appear, it might best be left unclassified until future studies elucidate its nature.

DISCUSSION

Rapid clinical onset of Cushing's syndrome does not necessarily imply that the disease process, *per se*, is of rapid onset. In fact, the evidence in-

dicates that the opposite is true. Renal stones must have been forming for some time in the two patients who were in good health until renal colic and facial edema initiated the syndrome. In fact, one of these patients was examined in our surgical department six months previously, at which time it was noted that he was in good health except for symptoms referable to a pilonidal sinus. It was also noted in retrospect that his blood pressure was 142 mm. systolic and 88 mm. diastolic, and that he had polycythemia and leukocytosis with lymphopenia, and glycosuria, 1 plus. A third patient in this series, whose intravenous pyelogram was normal, experienced a remission following pituitary irradiation. Four years later she gave birth to a child, two years after which she had renal colic. Two years later she returned to the clinic because of symptoms indicating recurrence of Cushing's syndrome. In this case, although the patient was "in remission" clinically, the steroid output must have been abnormally increased to cause the higher degree of calciuria which is the precursor of calculus formation. In a fourth patient, "in remission" following pituitary irradiation, a bleeding duodenal ulcer developed and a cerebrovascular accident occurred two years after therapy. In a fifth patient, described earlier in this paper, stress precipitated temporary hirsutism and amenorrhea, five and two years, respectively, before clinical onset with perforation of a duodenal ulcer.

The formation of renal calculi, the occurrence of bleeding duodenal ulcers and previous hematologic changes and glycosuria in the cases mentioned all support the concept that the disease may be active while the patient is symptomless, either before the clinical onset or during a clinical remission. The term "rapid onset" is, then, purely clinical, but can be considered simply as a useful indication of diagnostic value.

It is known that patients with Cushing's syndrome show enormous variations in the excretion of steroids, as determined by serial excretory estimations.²⁷ It would seem correct, therefore, to state that the type of onset, course and manifestations of the disease at any given time will depend upon the amount and type of steroid secretion. A prolonged period of slight increase in steroid production by the adrenal glands may cause symptomless changes until the stress of a complication such as ulcer perforation or renal colic triggers more obvious signs by resultant increased secretion.

In view of these observations, it is important to be able to classify complete remission, especially in a case where such an undramatic measure as deep x-ray treatment to the pituitary is employed. It would seem that such cases could be classified only after repeated laboratory studies. The assessment of a clinical remission based on symptoms and the more obvious signs can be misleading, and this confusion probably accounts for the contradictory reports on the therapeutic value of pituitary irradiation in this disease.

CONCLUSIONS

Cushing's syndrome is a rare disease. Few groups in the country have reported a series of more than 50 cases. We stress that it is not the rarity

of the condition, however, but its curability that makes it a disease with which not only the endocrinologist but also every practitioner should be familiar. The possibility of fatality as a result of complications, and the irreversible changes that may occur, are stressed. A reappraisal of the first clinical signs is presented in the hope that the physician will be increasingly alerted to the possibility of the existence of this disease, and that an early laboratory evaluation and treatment will be sought in patients presenting these signs.

SUMMARY

The advances made in recent years in the laboratory assessment of adrenocortical function and in the confirmation of hyperfunction by adrenal surgery and its results have rendered the differentiation of Cushing's syndrome, based on the classic manifestations of the fully developed condition, inadequate for making early diagnosis.

The initial symptoms in 34 cases were reevaluated with a view to promoting earlier recognition and diagnosis. Contrary to previously held opinions, clinical onset was found to be rapid in 71% of the cases, and it did not indicate the underlying etiology.

The clinical differential diagnoses are discussed in relation to the clinical onset; in the majority of cases they do not conform with the standard textbook enumeration. Particular attention is paid to the occurrence of edema and to its distribution. Edema is presumed to occur as a result of the tendency to hypoproteinemia, hypernatremia and vascular fragility.

Evidence of activity of the disease before its *clinical* onset and during a remission is presented. This indicates the difficulty of classifying a patient in remission, and therefore of assessing the value of therapy, particularly such undramatic therapy as pituitary irradiation.

The complications of Cushing's syndrome are enumerated, and a discussion of recently described cases with peripheral neuropathy is included.

SUMMARIO IN INTERLINGUA

Le syndrome de Cushing es potentialmente mortal. Su devastaciones es in parte proportional al longor del tempore de su presentia. Per consequente il es importante diagnosticar iste condition al tempore de su declaration. Le classic aspecto clinic de illo e su diagnoses differential describite in le manuales pertine a stadios avante o tardive. Le symptomas e signos initial in 34 casos es evalutate pro determinar le quales inter illos es possibilmente de valor in promover plus prompte diagnoses. Contrari a opiniones mantenite in le passato, il esseva constatare que le declaration esseva rapide in 71 pro cento del casos, e isto non indicava necessariamente le subacente condition pathologic.

Le termino "declaration rapida" esseva definite como representante le typo de declaration observate in casos ubi le symptomas esseva satis dramatic pro causar le alertia tanto del paciente como etiam del medico. Edema facial, con o sin edema del gambas, esseva le plus commun signo initial in iste gruppo. Illo causava le consideration de un diagnose de un condition hypothyroide, nephritic o nephrotic, o allergic o cardiac. Le occurrentia de un rapido ganio de pesos es frequentemente

explicare como un simple caso de obesitate, mesmo quando le presentia de signos additional como amenorrhea o hirsutismo deberea esser recognoscite como indicios diagnostic. Parametros thyroide es usualmente conflictori, sed quando illos es considerate individualmente insimil con le presentia de perdita de peso, nervositate, e augmento del sudoration, illos es a vices capace a supportar le diagnose de hyperthyroidismo. Colica renal pote etiam esser le prime signo clinic e devenir responsabile pro le erronee diagnose de idiopathic calculo renal. Etiam psychosis occurre como gravamine de presentation, e tal pacientes deberea esser examinate pro altere indications del syndrome de Cushing.

Quando le morbo comencia insidiosamente—in tal casos on parla de un “declaration gradual”—un lista de manifestations individual de syndrome de Cushing que etiam pote esser attribuite a altere morbos es prendre in consideration in le diagnose differential. Iste manifestations include simple obesitate, hirsutismo familial, amenorrhoea psychogenic o emotional, osteoporosis postmenopausal o senil, hyperparathyroidismo, hypertension essential, diabete mellite, polycythemia o purpuras, e disturbaciones mental.

Le complications de syndrome de Cushing es etiam enumerate. In le curso del tempore, su effectos super le metabolismo de calcium e proteina pote devenir responsabile pro fracturas pathologic e calculos renal. Hypertension pote devenir un problema continue, mesmo quando le subjacente stato pathologic ha essite tractate adequately. Le ben-cognoscite susceptibilitate de contraher infectiones que characterisa iste pacientes es sublineata de novo. Ulcerationes peptic occurreva in 9 pro cento del pacientes. Iste incidentia non excede illo trovate in le population general. Tamen, in iste respecto le lector pote consultar le excellente revista de Kirsner.¹⁷ Finalmente, le apparition de multiple neuritis peripheric in tres de nostre casos es mentionate. Le symptomas e signos, que non es dissimile a illos vidite in le syndrome de Guillain-Barré o in neuropathia diabetic, es discutite in detailio.

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BACTERIOLOGIC CULTURE OF THE DISEASED HUMAN LIVER*†

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THE role of bacteria in the pathogenesis of liver disease is uncertain. In ascending cholangitis, bacteria frequently invade the liver; however, in other types of liver disease, bacterial invasion of the liver often has been postulated but has not been demonstrated. The action of intestinal bacteria in the production of experimental cirrhosis in rats has been studied,^{1, 2} but it is difficult to transfer these findings to human cirrhosis.

Postmortem liver and portal vein cultures in the human have grown out intestinal bacteria within 30 minutes after death.³⁻⁵ Cultures of the liver by means of the Vim-Silverman biopsy needle, peritoneoscopic biopsy, and biopsy at laparotomy in patients with cirrhosis, hepatitis, fatty livers and normal livers have occasionally contained bacteria.⁵⁻⁸ The organisms, however, were usually gram-positive bacteria which were considered to be contaminants. Patients with acute hepatic disease were generally excluded from these studies because operation and biopsy are contraindicated.

We have cultured the livers of 20 patients with various types of liver disease, including acute hepatic disease. A quantitative bacteria-counting method was used to help to differentiate contamination from infection, and an aspiration technic was utilized when biopsy was contraindicated.

MATERIAL AND METHODS

Twenty patients were studied on the wards of the Boston City Hospital. Thirteen had cirrhosis of the alcoholic, two had hepatolenticular degeneration, and one patient each had cirrhosis of the alcoholic and acute homologous serum hepatitis, cirrhosis of undetermined type and acute cholangitis, cirrhosis of undetermined type, fatty liver, and congestive hepatomegaly (table 1). In the 12 patients with temperatures over 100° F., the fever was presumably caused by chronic pulmonary inflammation in two, pulmonary tuberculosis in two, and staphylococcal pneumonia, tuberculous

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TABLE 1
Hepatic Cultures in 20 Patients with Liver Disease*

| Patient | Diagnosis | Daily Temperature Range | | Serum Bilirubin mg./100 ml. | Brom-sulphalein % Retention 45 Min. | Serum Albumin Gm./100 ml. | Serum Globulin Gm./100 ml. |
|---------|--|-------------------------|-------|-----------------------------|-------------------------------------|---------------------------|----------------------------|
| | | Min. | Max. | | | | |
| 1 | C.† of alcoholic, acute | 99.2 | 101.2 | 6.5 | — | 3.8 | 3.6 |
| 2 | C. of alcoholic, acute; acute pancreatitis | 97.6 | 100.6 | 5.8 | 23 | 3.2 | 2.5 |
| 3 | C. of alcoholic, acute | 98.4 | 101.4 | 48 | — | 4.2 | 3.4 |
| 4‡ | C. of alcoholic, acute; bronchopneumonia | 98.2 | 99.4 | 19.2 | — | 4.1 | 2.1 |
| 5 | C. of alcoholic, acute; pulmonary tuberculosis | 98.2 | 101.6 | 3.9 | — | 2.1 | 3.9 |
| 6 | C. of alcoholic, acute; serum hepatitis | 97.0 | 107.4 | 17.4 | — | 4.2 | 4.7 |
| 7 | C. of alcoholic, chronic; bronchopneumonia | 99.2 | 103.6 | 3.6 | — | 2.4 | 4.4 |
| 8 | C. of alcoholic, chronic; chronic cholangitis; tuberculous peritonitis | 100.6 | 105.4 | 1.5 | — | 4.4 | 2.8 |
| 9 | C. of alcoholic, chronic | 98.6 | 99.8 | 1.0 | 8.8 | 3.7 | 2.3 |
| 10 | C. of alcoholic, chronic | 97 | 98.6 | 1.4 | 25 | 3.7 | 2.7 |
| 11 | Fatty liver; silicosis | 98.2 | 101.0 | — | 9.8 | 4.1 | 3.1 |
| 12 | C. type undetermined; acute cholangitis | 97.6 | 103.0 | 5.3 | 6.4 | 3.6 | 3.9 |
| 13 | C. of alcoholic, chronic; miliary tuberculosis | 99.8 | 103.0 | 1.3 | 21 | 3.1 | 2.5 |
| 14 | C. type undetermined | 98.2 | 99.6 | 0.9 | 7.8 | 4.1 | 2.9 |
| 15 | Congestive hepatomegaly; bronchiectasis; pulmonary embolism | 98.6 | 100.8 | 0.6 | 28 | — | — |
| 16 | C. of alcoholic, chronic; pulmonary tuberculosis | 98.8 | 100.4 | 1.0 | 34 | 4.1 | 3.0 |
| 17§ | C. of alcoholic, acute; pulmonary tuberculosis | 97 | 99.8 | 4.7 | — | 4.1 | 2.9 |
| 18 | C. of alcoholic, chronic; chronic bronchitis | 98.6 | 100.0 | 0.7 | — | 4.6 | 3.9 |
| 19 | Hepatolenticular degeneration | 97.8 | 98.6 | — | — | 5.5 | 1.9 |
| 20 | Hepatolenticular degeneration | 98.2 | 99.4 | 0.2 | 1.2 | 4.5 | 2.3 |

* There was no growth in the cultures except for *E. coli* from case 12. See text. Cases 1 through 7 all had hepatic coma or precoma, and aspiration culture was used.

† C. = Cirrhosis.

‡ Receiving oral neomycin.

§ Receiving oral isonicotinic acid hydrazide and para-aminosalicylic acid.

peritonitis, acute cholangitis, miliary tuberculosis and acute pancreatitis in one each. In two patients acute hepatic decompensation with cirrhosis and necrosis was the only evident explanation. In one of these patients this impression was confirmed at autopsy. One patient had subacute yellow atrophy which was felt to be secondary to homologous serum hepatitis.

Cultures were obtained either from a Vim-Silverman needle biopsy specimen (14 patients) or by aspiration (six patients), using a No. 20 spinal puncture needle. Aspiration culture was used when liver biopsy was contraindicated, i.e., when there was low blood prothrombin activity or poor

patient coöperation. In the latter instances, standard biopsy technic was used with iodine and alcohol preparation of the skin. When the stylus was removed, a 20 ml. syringe was attached, the needle was advanced into the liver, and suction was applied for about four seconds. A few drops of fluid were obtained and introduced into 3 to 5 ml. of the culture medium by rinsing the syringe once with sterile broth.

The culture media used were beef heart infusion broth with 5% horse blood, and chopped meat media for anaerobic cultures. The inoculated media were plated in nutrient agar and counted, were diluted immediately in serial one hundred fold dilutions for bacterial count, and were also incubated for from one to four days. If the incubated media showed evidence of growth, they were then subcultured and the subcultures were serially diluted by one hundred fold dilutions in nutrient broth, aliquots of the dilutions being plated in nutrient agar and counted. A loopful of each culture was also streaked on blood agar and eosin methylene blue agar. Previous use of quantitative technics in the analysis of urinary tract infections had indicated that separation between contamination and infection may often be achieved on the basis of bacterial numbers in the urine.⁹ It is hoped that this method may also distinguish contamination from infection for liver cultures.

BACTERIOLOGIC OBSERVATIONS

Bacteria were recovered from the liver in only one instance, and a colony count of over 100,000 per milliliter suggested that it did not represent contamination. The organisms were identified as *Escherichia coli*. This patient was a chronic alcoholic with anorexia, weight loss, mild jaundice and an intermittent spiking fever. A Vim-Silverman biopsy and culture were performed, and a diagnosis of mild cirrhosis with portal inflammation was suggested. Laparotomy later confirmed the presence of acute and chronic cholecystitis with common duct stones and cholangitis.

COMMENT

The mechanisms for clearing bacteria which enter the bloodstream are, in part, a function of the fixed macrophages of the reticuloendothelial system (i.e., Kupffer's cells of the normal liver) and the circulating leukocytes.¹¹ Libman postulated in 1908 that certain infections (e.g., liver abscess, cholecystitis, appendicitis, peritonitis, and pylephlebitis) rarely show positive blood cultures because they are all located in an area drained by portal vein tributaries, permitting removal of bacteria by the liver.¹⁰ Spontaneous bacteremia due to organisms which normally inhabit the intestine has been reported in patients with Laennec's cirrhosis,^{12, 13} and we have made similar observations. This assumed passage of intestinal bacteria into the general circulation in cirrhosis might conceivably be related to the presence of shunts by-passing the liver, or to impairment of the hepatic reticuloendothelial system.

In addition to severe hepatic fibrosis, other causes of increased shunting of blood around the liver might include contraction of hepatic sinusoidal sphincters, as described by Knisely.¹⁴ Indeed, intravenous injections of endotoxin from *E. coli* and *Brucella melitensis* in anesthetized dogs have been observed to produce hepatic congestion and a marked rise in portal vein pressure, with pooling of blood in portal tributaries.¹⁵

The escape of intestinal bacteria into the portal vein and liver is well known in experimental animals; antibiotics have made survival possible under conditions which would otherwise have produced severe liver injury and death.^{16, 17} Ligation of the hepatic artery in dogs is followed by growth of anaerobic clostridia in the anoxic liver. However, it is unlikely that this occurs in man,¹⁸ and bacteria have been demonstrated conclusively in the human portal vein and liver only in postmortem cultures or in the presence of biliary tract disease.

Two reports of human portal vein cultures have been contradictory. Schatten et al.¹⁹ obtained bacteria from the portal vein in 33% of patients studied at operation. Many of these patients had biliary tract disease, and these authors concluded that there is continual seeding of the portal vein with intestinal bacteria. Taylor²⁰ found bacteria in 6% of portal vein blood cultures taken through a plastic tube that was left in place following surgery. He suggested that the portal vein blood is ordinarily sterile. The failure to find bacteria in the portal blood and the presence of intestinal bacteria in mesenteric lymph nodes²¹ are in accord with the probability that the entry of intestinal organisms into the bloodstream is by way of the lymphatics, rather than directly into the circulation.¹¹

Previous reports of human hepatic cultures have indicated that the normal liver does not ordinarily contain bacteria. Romieu and Brunschwig⁶ cultured the livers of 12 patients at operation for lower abdominal neoplasm and found bacteria in but two instances: one a diphtheroid (considered a contaminant), and the other a *Pseudomonas* which was also cultured from the wound and from bladder urine. Sborov et al.⁵ obtained two positive cultures from the livers of 66 patients with hepatic disease. Both cultures were obtained from the left lobe of the liver at laparotomy, and consisted of one klebsiella-like organism and one fungus. Perry et al.⁷ obtained two positive cultures of *Staphylococcus aureus* (coagulase-negative) from the livers of 39 patients at laparotomy; both were considered to be contaminants. From and Alli⁸ obtained 13 positive cultures (all *S. aureus* or diphtheroids) from 101 liver cultures taken through a peritoneoscope; all were considered to be contaminants. Thus, it has been suggested that bacteria may invade the portal vein only at times of unusual physiologic stress, such as surgery, shock, anoxia or abdominal trauma.⁵

Little bacteriologic evidence is available in acutely decompensated cirrhosis or in hepatic coma, as these patients are notably poor operative risks for either laparotomy or needle biopsy. Many of the clinicopathologic

features of patients with hepatic decompensation are those usually attributed to acute infection (i.e., fever, leukocytosis, polymorphonuclear leukocyte infiltration of the liver, shock). Administration of nonabsorbable antibiotics in hepatic coma is associated with improvement, although this may be due to decreased intestinal ammonia production.²²

Our results in a small series of cultures, including patients with acute hepatic decompensation, fever, hepatic coma, and demonstrated pulmonary infections, are in agreement with the hypothesis that bacteria are actively involved in human liver disease only when there is associated biliary tract disease. The one positive culture in our series occurred in a patient with previously unsuspected subacute cholangitis and cholecystitis.

SUMMARY

Culture of the liver was performed in 20 patients with various types of acute and chronic liver disease. Cultures were obtained from biopsy specimens, and from aspiration of the liver when biopsy was contraindicated. A quantitative counting method was used to differentiate contamination from infection. The one positive culture was obtained from a patient with a common duct stone and ascending cholangitis.

The data that are presently available suggest that bacteria are not ordinarily found in the human liver or portal vein blood, but that bacteria may invade the portal vein under unusual physiologic circumstances, such as abdominal trauma, surgery, irradiation, shock, anoxia, or other circumstances leading to local changes in the intestinal wall. Why biliary stasis is particularly related to the retention of bacteria in the liver is not yet clear.

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SUMMARIO IN INTERLINGUA

Culturas de hepate esseva effectuate pro 20 pacientes con acute e chronic morbo hepatic, incluse pacientes con infection acute e con febre sin explicacion apparente. Le culturas esseva obtenite ab specimenes biotic o—in caso de contraindication de biopsia—ab specimenes aspirate. Un metodo de contation quantitative, basate super dilutiones serial de medios cultural aerobie e etiam anaerobie esseva utilitate pro differentiar inter contamination e infection. Un cultura positive esseva obtenite solmente ab un paciente. Ille habeva calculo de via biliar commun e cholangitis ascendente. In iste caso, un contation de plus que 100.000 colonias de *Escherichia coli* per millilitro de medio cultural initial pareva significar que il non se tractava de un contamination.

Iste resultatos es de accordo con previe reportos de culturas tanto de hepate como etiam de vena portal e pare indicar que bacterios non es ordinariamente trovate in le hepate human o in le sanguine del vena portal. Tamen, il remane possibile que bacterios invade le hepate sub unusual circumstantias physiologic, como per exemplo in caso de trauma abdominal, de intervention chirurgic, de irradiation, de choc, de anoxia, o de altere factores que resulta in alteraciones local in le pariete intestinal.

Bacterios ha essite culturate ab le hepate de pacientes con morbo del vias biliari. Tamen, il es non ancora clar proque stasis biliaris es particularmente relationate con le retention de bacterios in le hepate. In septe pacientes con le acute cirrhosis del alcoholicos e con hyperbilirubinemia nulle culturas positive esseva obtenite.

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SYMPTOMS AND PATIENTS' ADJUSTMENT AFTER SUBTOTAL GASTRECTOMY *

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INTRODUCTION

RESULTS of gastric resection for peptic ulcer are said to be good in 85 to 90% of cases. Our results have also been good in that almost all of our patients have had no further symptoms or complications due to peptic ulcer, but they have had symptoms due to their gastrectomy. Often these have been mild, or the patient has adjusted to them so completely that he does not even mention them unless questioned specifically. When patients are carefully questioned, however, it becomes apparent that many have symptoms subsequent to surgery, and that these often influence their ability to work, their energy for leisure time activities, and their diet.

METHOD

One hundred unselected male patients who had had elective partial gastrectomy at the Cleveland Veterans Administration Hospital between 1951 and 1955 were studied before and one year after operation.

The patients' ages ranged from 25 to 65; 64 were between 30 and 49. Fifty-nine had not completed high school; none had been graduated from college. Seventy-one patients were married; 17 others were separated or divorced. Forty-eight patients were receiving a pension or were eligible for free medical care because their ulcers had been incurred in the military service. Most patients were in the lower income brackets, a few in the middle. They were cooks, taxi-drivers, truck-drivers, laborers, construction workers, mill hands, skilled workmen and salesmen; there was one internal revenue agent.

None of the operations in this group was done as an emergency. Fifty-nine patients with duodenal ulcer were operated upon because of recurring symptoms of ulcer. All of them had had at least one previous course of medical management in a hospital. Sixteen patients with duodenal ulcer were operated upon for pyloric obstruction, and 11 others because they had had hemorrhages or perforations, or both, and it was feared that these might recur. Of the 12 patients with gastric ulcer, six were operated upon for recurrent ulcer, four because their ulcers failed to heal after several weeks

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of treatment, and two for pyloric obstruction. Two patients were operated upon for marginal ulcers which followed gastrojejunostomy. All patients had an estimated 75% resection with anastomosis by a modified Billroth II technic.

All patients were interviewed preoperatively by each of the three authors—an internist (H. P. R.), a surgeon (C. L. C.), and a medical social worker (H. M. O.). Postoperatively at least two of the authors interviewed every patient. The medical social worker made a careful study of the work record of each patient. The following subjects were covered in the preoperative and postoperative interviews:

A. Work Record

1. Length of convalescence before returning to work.
2. Jobs during five years before and first year after operation.
3. Changes in pay, with reason.
4. Time lost during three years before and first year after operation, with reasons.

B. Diet

1. Frequency of eating and amount eaten per meal after operation.
2. Foods avoided and tolerance for milk or sweets after operation.

C. Dumping syndrome (includes symptoms attributable to a small stomach, and defined as a symptom complex occurring immediately after meals and including one or more of the following: weakness, nausea, a feeling of distention, a feeling of warmth, vomiting, sweating, or palpitation). Symptoms were classified as mild if they had not interfered with work or usual activities, moderate if they occasionally interfered, severe if they frequently interfered.

D. Fatigue and weakness.

E. Complaints other than gastrointestinal.

F. Medicines taken after operation, with reasons.

G. Frequency of visits to physicians.

H. Alcoholism, defined as drinking to an extent that interfered with the patient's work or usual activities.

I. Pension status.

RESULTS

Many patients did not return to work as early as seemed medically feasible. If time spent in the hospital is excluded, three months of convalescence were considered to be adequate for a patient engaged in physical labor, six weeks for one not doing physical labor. Applying these criteria, we found that, of the 69 patients on whom data were available, 15 laborers and 11 others had spent more than a reasonable period convalescing.

Forty-eight patients changed jobs after gastrectomy. Thirty-two of these received a lower wage. Nineteen of the latter changed jobs because of symptoms that appeared after gastrectomy, usually weakness and excessive fatigue, but in a few instances because of dumping symptoms. The remaining 13 patients had taken lower-paying jobs for reasons not directly related to their gastrectomy—dissatisfaction with previous jobs, work not available, or alcoholism; several patients near retirement stopped regular work and took part-time jobs.

Those patients who returned to work lost less time than before their gastrectomy (table 1). Thirty-six patients, however, lost a significant amount of time during their first year after operation. Twenty-four attributed this to postgastrectomy symptoms, particularly fatigue and weakness.

At follow-up, 11 patients had not been working. Five had not been working before operation, and three had been working only irregularly. Of

TABLE 1
Time Lost from Work

| Time Lost/year | Before Operation | | After Operation | |
|-------------------|------------------|--------------|--------------------------|--------------|
| | Ulcer Symptoms | Other Causes | Postgastrectomy Symptoms | Other Causes |
| Less than 1 week | 9 | 2 | 10 | 2 |
| 1-3 weeks | 26 | 1 | 10 | 3 |
| More than 3 weeks | 54 | 10 | 24 | 12 |
| None | | 6 | | |
| Unknown | | | 39 | 5 |

Some patients who lost time from work for ulcer symptoms or postgastrectomy symptoms also lost time for other causes.

the remaining three patients, two had retired at ages 57 and 62, complaining of fatigue, dumping symptoms and nervousness. The last patient, 28 years old, had had similar complaints but these did not explain his failure to return to work.

Ten patients did only odd jobs after operation. Four of these patients, two of them alcoholics, had not been working regularly before operation. Two more patients had been laid off after operation and claimed that they could not find new jobs. Two others, 55 and 60 years old, having recently lost their wives, appeared to have no incentive to do more work than necessary for subsistence. The remaining two patients were an alcoholic and a severe psychoneurotic.

Fatigue and weakness were common complaints after operation. Many patients complained that these symptoms interfered with work or social activities (table 2). Fifty-six patients indicated that fatigue first appeared or increased after operation, five reported a decrease, and 37 no change.

TABLE 2

Fatigue

| | Before Operation | After Operation |
|-------------------------------|------------------|-----------------|
| No fatigue | 56 | 28 |
| Fatigue interfering with work | 14 | 35 |
| Excessive fatigue after work | 11 | 35 |
| Fatigue unqualified | 14 | 19 |
| No information | 3 | 2 |

Some patients appear in more than one category.

After gastrectomy, 51 patients avoided various foods because they caused gastrointestinal symptoms. Thirty avoided milk or milk products, 23 sweets, particularly desserts, 11 fried, fatty or greasy food, and a few spaghetti, pineapple, cocoanut, eggs, cereal and chili. Eight patients occasionally followed an "ulcer diet."

Only one patient developed a marginal ulcer during the follow-up period. Patients saw doctors for gastrointestinal symptoms much less frequently after gastrectomy than before (table 3). Only nine patients saw a doctor regularly (12 or more times a year) after operation. Of these, four had been seeing a physician regularly before operation, and four others had been seeing a physician frequently (from five to 11 times a year). Six additional patients saw doctors frequently for conditions not related to the gastrointestinal tract. These included alcoholism, backache, fracture, goiter and nervousness.

Fourteen patients took antacids or antisecretory drugs after gastrectomy for symptoms consistent with the dumping syndrome, or for ill defined epigastric distress. Six patients took iron and vitamin preparations for fatigue. One patient took phenobarbital for nervousness.

Following operation, 50 patients complained of dumping symptoms. In 30 the symptoms were mild, in 17 moderate and in three severe. Seventeen patients had occasional episodes of mild abdominal pain; in only one case was this suggestive of ulcer.

At follow-up, 21 patients presented new complaints not referable to the gastrointestinal tract. These complaints included chest pain, leg cramps, prostate trouble, sore feet, backache, hemorrhoids, shortness of breath, fever, cough, frequent colds, heart trouble and tuberculosis. In one patient cirrhosis became worse after operation, and in another, headache.

Thirteen patients had been alcoholics before operation. After operation,

TABLE 3
Patient Visits to Physicians for Gastrointestinal Symptoms

| Frequency of Visits (except scheduled follow-up) | Before Operation | After Operation |
|---|------------------|-----------------|
| Never | 0 | 71 |
| Less than 5 times/year | 60 | 15 |
| 5-11 times/year | 25 | 5 |
| 12 or more times/year | 15 | 9 |

four of these stopped drinking, two others increased their drinking. Six additional patients started drinking heavily.

The difficulty following gastrectomy due to both dumping symptoms and weakness or fatigue was evaluated. For this analysis, limiting the amount of food eaten at a single meal or avoiding certain foods was disregarded, as these symptoms were considered to be of minor importance. Thirty-seven patients had no symptoms that interfered with their regular activities, 20 had symptoms that occasionally did, and eight had symptoms that frequently interfered.

Forty-eight patients were receiving either pensions or free medical care for an ulcer incurred in or aggravated by military service. There was no correlation between service connection and poor results as indicated by delay in return to work, stopping work, taking a job with less pay, undue fatigue or weakness, severe dumping symptoms, excessive nervousness, or seeing doctors frequently after operation.

DISCUSSION

Recurrence of ulcer symptoms after gastric resection was not a problem in this group of patients. There were, however, other symptoms following operation that affected patients' work and leisure time activities. These symptoms have been mentioned by a few authors, but they have not been considered in many studies, as the results of gastrectomy have usually been evaluated in terms of relief of ulcer symptoms, frequency of dumping symptoms, and incidence of weight loss.

Fatigue and weakness were such important postgastrectomy symptoms that they often interfered with work or social activities. They appeared or increased after operation in 56 patients. These symptoms were referred to by a few other investigators,^{1, 2} but their frequency was emphasized only by Warren and Meadows,³ who reported an incidence of 38.8%, and by Rauch,⁴ who reported 61%. Ross and Walsh⁵ remarked that diminution of strength does not appear to have been commented on by previous writers, probably because it has not been specifically sought.

About one third of our patients took jobs with less pay after gastrectomy. Nineteen indicated this was due to postgastrectomy symptoms, usually weakness and excessive fatigue. Other authors noted that some patients reported a diminished capacity for work after gastrectomy.^{1, 4-9} Van Goidsenhoven et al.¹⁰ said that only about half of their patients felt that their capacity for work was as great after operation as before. Several authors specifically stated that their patients tired easily^{1, 4, 5} or required lighter jobs.^{6, 9, 11} In our experience, few patients gave dumping symptoms as the cause for taking lighter work, which is in contrast to the experience of Bell et al.⁷ and Custer et al.⁸

A few patients indicated that they had changed their jobs not because of postgastrectomy symptoms but for other reasons. Some preferred a job

with less responsibility, while others did not like their old jobs. The operation provided a justification for the previously desired change. A few were laid off.

In general, patients worked more regularly after operation, and many had a larger take-home pay, even though some had taken lower paying jobs.

Somewhat over a third of our patients took longer than the six weeks for sedentary workers or three months for laborers that Gaviser¹² indicated was the usual convalescent period in his group. Anderson et al.⁶ also noted that over a third of their patients failed to return to work in three months, but Porter¹³ found that only 16% of his patients required more than three months for convalescence.

Twenty-one per cent of our patients were not working regularly after surgery. This is a considerably higher incidence than that reported by Custer et al.⁸ (1.2%), Van Goidsenhoven et al.¹⁰ (2.9%), Anderson et al.⁶ (3.6%), Gaviser¹² (5.8%), and Bell et al.⁷ (13.4%).

Of these 21 patients, 13 failed to work regularly for reasons unrelated to their gastrectomy. Four more patients were in an older age group, and we noted that older patients were inclined to retire or to do only odd jobs after surgery. Metcalf et al.¹⁴ commented on the tendency of older patients to retire, which they ascribed to decreased work capacity following operation.

Dumping symptoms were common (50%) in this series, as they have been in many others,^{3, 4, 7, 14, 16} but were severe in only three cases. The symptoms improved in many patients as they learned to adjust their eating habits, a point that has been emphasized by Meurling.¹⁵ Restriction of food intake to avoid dumping symptoms may account for the weakness and weight loss many patients show. This may have been particularly striking in our patients, as a majority of them were laborers and required a large caloric intake.

Certain foods commonly produced symptoms after gastrectomy. Twenty-one patients reported having dumping symptoms after milk or milk-containing foods, and 19 after sweets. Meurling¹⁵ reported that 47% of his patients had symptoms after milk or milk-containing food, and 20% after sweets. Rauch⁴ found 52% of his group was unable to tolerate milk, ice-cream or rich desserts. Some of our patients complained of distress after fatty or fried foods, onions, cabbage, condiments, chili, turnips and cucumbers, but these foods may cause distress in individuals who have not had a gastrectomy.

Some psychiatrists have hypothesized that the relief of peptic ulcer symptoms by surgery may result in the development of new symptoms^{2, 16} as an outlet for emotional tensions.¹⁷ In our series, some patients did develop new symptoms, but these usually seemed to have an organic basis.

The pension status of the patient did not appear to influence the results of his surgery for ulcer. This was also noted by Jordan and DeBakey.¹⁸

SUMMARY

One hundred patients were studied before and one year after elective subtotal gastrectomy for peptic ulcer. The group as a whole worked more regularly after operation. Twenty-one patients did not work or did no steady work after operation, but most of these had had a poor work record before operation. About a third of all patients took lower paying jobs. Fatigue and weakness were the most important complaints after gastrectomy. Dumping symptoms per se were not a major cause of disability.

SUMMARIO IN INTERLINGUA

Un cento patientes esseva studiate ante e un anno post elective gastrectomia subtotal pro ulcer peptic. Solmente un del patientes disveloppava un ulcer marginal durante le periodo de observation, e le patientes consultava lor medicos multo minus frequentemente pro symptomas gastrointestinal post le gastrectomia que ante illo.

Fatiga e debilitate esseva si importante como symptomas postgastrectomic que illos obstrueva frequentemente le labores professional e le activitates social del subjectos. Symptomas de vacuation immediate esseva commun in iste serie de casos (50%), sed illos esseva sever in solmente tres.

Le restriction del ingestion de nutrimentos, acceptate pro evitar le symptomas del vacuation immediate, es possibilmente responsabile pro le debilitate e le perdita de peso de multes del patientes. Lacte e dulces esseva le nutrimentos que produceva le symptomas le plus frequentemente.

Vinti-un patientes travaliava non del toto o non regularmente post lor gastrectomia, sed le majoritate de istes habeva travaliate irregularmente etiam ante le intervention chirurgic. Patientes de etate plus avantiate monstrava le tendentia de retirar se o de acceptar solmente travalios de occasion post le operation. Circa un tertio del patientes acceptava post le operation un position a salario reducite.

In le consultationes postoperatori, certes del patientes presentava nove gravamines non associabile con le vias gastrointestinal, sed istos habeva usualmente un base organic.

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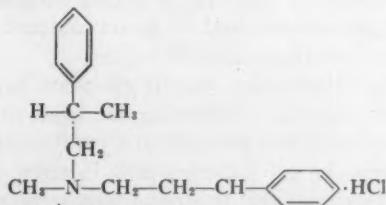
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EFFECTS OF A NEW "CORONARY VASODILATOR" ON THE GENERAL AND CORONARY HEMO- DYNAMICS AND MYOCARDIAL METABO- LISM OF MAN * †

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THE continued pharmacologic search for drugs capable of producing a positive increase in the coronary blood of man is an important phase in the management of patients with coronary artery disease. It is a distressing fact that many substances which pharmacologically appear to be promising later fail to fulfill this promise in the course of direct clinical trial. The clinical use of such "vasodilator" substances is often predicated upon the physiologic observation that they produce an increased coronary blood flow in animal preparations, without considering the possibility that the increase in flow may represent solely a heightened myocardial demand induced by the administered chemical.* Furthermore, since purely subjective evaluation of new treatments by patients may be unreliable even with the double-blind approach, it is desirable that such substances be evaluated objectively in the clinical laboratory before they are released for clinical trial. The following studies were designed to test the hemodynamic effects of such a substance on the general and coronary circulation of man.

Vasoflex ‡ (N-cinnamyl-methylamino-2-phenylpropane hydrochloride) is a new synthetic substance chemically related to the catechol amines, with the following structural formula:



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‡ Vasoflex is the trademark of the Wm. S. Merrell Co., Cincinnati, Ohio. It was supplied as a parenteral solution containing 5 mg./ml.

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It has been characterized pharmacologically by Ahlquist and associates.¹ Injected intra-arterially, it produces peripheral vasodilatation, as evidenced by decreased vasomotor resistance in the femoral, uterine, renal and carotid arteries of anesthetized dogs. Coronary inflow is increased in the isolated Langendorf cat and rabbit heart preparations.

Kien, Gomoll and Sherrod¹¹ have shown that, in anesthetized dogs, parenteral administration of the drug (0.5 to 5 mg./kg. body weight), given as a single dose, increases coronary sinus outflow and coronary artery inflow by as much as 75% for periods ranging from 10 to 45 minutes. The smaller dose is almost as effective as the larger. The increased flow is associated with no significant change in the heart rate and the peripheral arterial pressure.

These findings in animals are sufficiently encouraging to warrant consideration of the possible beneficial effects of Vasoflex in humans. The present study was designed to determine whether this drug has effects on the circulation and metabolism of the heart in man which would indicate that it produces a *real* increase in the supply of oxygen to the myocardium.

MATERIALS AND METHODS

Studies were conducted in three groups of subjects:

1. *Electrocardiographic and Blood Pressure Studies:* The effect of as much as 0.5 mg./kg. of body weight on the heart rate and arterial blood pressure was noted in 14 subjects in the recumbent position. These patients either were free of heart disease or had enlarged hearts due to hypertension or coronary artery sclerosis. The heart rate was determined electrocardiographically and the brachial artery pressure sphygmomanometrically every two minutes for 30 minutes. The drug was then administered intravenously during a period of three minutes, and the heart rate and blood pressure were recorded every minute for 45 minutes thereafter.

2. *Cardiac Output Determinations:* Right-sided cardiac catheterization was performed in six patients. Following the basal determinations of pulmonary and intrabrachial artery pressure and cardiac output (Fick principle with oxygen), 0.5 mg./kg. of Vasoflex was injected intravenously in the manner described above, and the determinations were repeated immediately after and eight minutes after the completion of the injection. All data were obtained in duplicate.

3. *Coronary Blood Flow Studies:* The coronary sinus was catheterized according to the technic of Goodale and associates¹⁰ in eight subjects. Coronary flow measurements, employing the nitrous oxide desaturation method,⁹ were done as single determinations during a basal control period and following the intravenous injection of the drug. Brachial artery and coronary sinus blood samples were analyzed for oxygen and for glucose,¹³ lactate² and pyruvate.⁸ The total left ventricular utilization of these substances per

TABLE I
General Hemodynamic Effects of Intravenous Injection of Vasoflex. Data gathered during control (C) period, and 8 minutes following completion of injection (E)

| Patient, Color, Sex, Age | Diagnosis | Control Expt. | H.R./min. | P_{Ba} , mm. Hg | P_{Sa} , mm. Hg | BMR _{O₂} , c.c./min. | A.V. Diff. vol. % | C.O., c.c./min. | LVW, kg/m/min. | P.U.T.R., c.g.s., units | ETPR, c.g.s., units |
|--------------------------|----------------------------------|---------------|-----------|------------------------------|--------------------------|--|-------------------|-----------------|----------------|-------------------------|---------------------|
| P C WM 63 | Hypertension, CVA | C E | 53 65 | 196/78 (112) 225/90 (134) | 34/14 (21) 48/21 (32) | 156 200 | 5.31 46.7 | 2850 4284 | 4.31 7.72 | 590 606 | 3140 2490 |
| J G NM 47 | Postpneumonia, cirrhosis | C E | 100 108 | 116/71 (88) 116/73 (88) | 20/13 (18) 20/15 (18) | 304 302 | 3.88 3.76 | 7835 8032 | 9.30 9.50 | 181 174 | 902 875 |
| C F NM 59 | Pulmonary emphysema | C E | 98 106 | 123/79 (95) 118/74 (92) | 43/30 (35) 39/26 (33) | 136 156 | 7.31 6.08 | 1860 2560 | 2.40 3.20 | 1482 1007 | 4081 2849 |
| S J NM 62 | Coronary artery disease, failure | C E | 80 80 | 129/73 (89) 130/73 (89) | 50/20 (28) 48/21 (29) | 106 180 | 5.26 5.14 | 2040 3510 | 2.45 4.20 | 1097 666 | 3485 2043 |
| R S WM 69 | Post bronchopneumonia | C E | 80 78 | 163/73 (106) 158/71 (103) | 34/15 (23) 28/12 (18) | 234 237 | 3.56 3.43 | 6600 6915 | 9.40 9.60 | 285 208 | 1282 1192 |
| J R. WM 28 | A-V fistula of brain | C E | 63 60 | 125/81 (97) 125/79 (96) | 22/15 (18) 21/14 (18) | 271 266 | 4.47 4.29 | 6060 6220 | 7.90 8.10 | 237 233 | 1279 1242 |
| Averages | | C E | 79 83 | 142/76 (98) 145/77 (100) | 34/18 (24) 34/18 (24) | 201 223 | 4.97 4.56 | 4541 5254 | 5.96 7.05 | 645 482 | 2361 1782 |
| $P =$ | | <.2>.1 | | <.7>.6 | | <.2>.1 | | <.1>.05 | | <.05>.02 | |
| | | <.2>.1 | | <.7>.6 | | <.2>.1 | | <.1>.05 | | <.2>.1 | |

Key—From left to right, heart rate, brachial artery pressure, pulmonary artery pressure (mean pressures in parentheses), oxygen consumption, arteriovenous oxygen difference, cardiac output, left ventricular work, total pulmonary resistance and systemic vascular resistance. "*p*" values according to Fisher's "*t*" test, groups less than 30.

TABLE 2
Coronary Hemodynamic Effects of Intravenous Injection of Vasoflex. Data gathered during control (C) period, and during 10 minute period following completion of injection (E)

| Patient, Color, Sex, Age | Diagnosis | Control Expt. | H.R./min. | MABP mm. Hg | CF c.c./100 gm./min. | BAO ₂ vol. % | CSO ₂ vol. % | BA-CO ₂ A-V Diff. vol. % | VMRO ^a c.c./100 gm./min. | % Ext. (a-v/a) | CVA Res. Units ^b |
|--------------------------|---------------------------------|---------------|-----------|-------------|----------------------|-------------------------|-------------------------|-------------------------------------|-------------------------------------|----------------|-----------------------------|
| H. G. NM 54 | CVA | C | 89 | 100 | 93 | 18.4 | 5.0 | 13.4 | 12.5 | 73 | 1.1 |
| C. H. NM 49 | Postpneumonia | C | 92 | 100 | 205 | 19.0 | 4.8 | 14.2 | 29.2 | 75 | 0.5 |
| L. C. NM 34 | Postpneumonia | E | 80 | 96 | 96 | 13.2 | 1.5 | 11.7 | 11.2 | 89 | 1.0 |
| L. K. WM 51 | Bronchogenic carcinoma | E | 81 | 96 | 132 | 13.4 | 2.4 | 11.0 | 14.5 | 82 | 0.7 |
| C. J. WM 36 | Cirrhosis | C | 66 | 86 | 73 | 18.6 | 6.7 | 11.9 | 8.7 | 64 | 1.2 |
| R. S. NM 31 | Femoral a/v fistula | E | 66 | 101 | 106 | 18.7 | 6.3 | 12.4 | 13.2 | 66 | 1.0 |
| J. G. WM 74 | Coronary disease, enlarged L.V. | C | 94 | 75 | 124 | 13.6 | 5.3 | 8.3 | 10.3 | 61 | 0.6 |
| J. B. NM 66 | Postpneumonia, hypertension | E | 102 | 71 | 123 | 13.5 | 5.3 | 8.2 | 10.1 | 61 | 0.6 |
| Averages | | C | 72 | 92 | 84 | 15.1 | 3.1 | 12.0 | 10.1 | 79 | — |
| p = | | E | 74 | 95 | 160 | 14.9 | 3.0 | 11.9 | 19.1 | 80 | 0.6 |
| | | | | | | | | | | 70 | — |

Key—From left to right, heart rate, mean brachial artery pressure, coronary ("left ventricular") blood flow, brachial artery oxygen content, coronary sinus oxygen content, brachial-coronary sinus oxygen difference, myocardial ("left ventricular") oxygen uptake, oxygen extraction coefficient, coronary vascular resistance.

minute could then be determined as the product of the coronary blood flow and the coronary arteriovenous difference. The percentage extraction by the myocardium could then be calculated by dividing the coronary arteriovenous difference by the arterial level (i.e., $\frac{A-V}{A} \times 100$).

RESULTS

1. *Electrocardiographic and Blood Pressure Studies:* In 11 patients there was virtually no change in the heart rate and the brachial arterial pressure. In two patients there was a transient rise in the systolic and diastolic pressures which returned to control levels within a few minutes after completion of the injection; in one of these patients the rise in blood pressure was accompanied by a decrease in the heart rate. In the remaining subject an intermittent 2:1 heart block was replaced by normal conduction during the injection, and this lasted for the remaining period of observation.

2. *Cardiac Output Determinations:* There was no significant difference between the data obtained immediately after and eight minutes after injection. The control and "eight minute" experimental data are shown in table 1.

There was no significant change in the *heart rate* or the *brachial and the pulmonary artery pressures*. Although the *systemic oxygen consumption* and the *arteriovenous oxygen* difference did not change significantly, the respective directional increase and decrease resulted in increases of the *cardiac output* and the *calculated left ventricular work* which were of borderline statistical significance ($p = <.05>.02$). The average *total pulmonary* and *systemic vascular resistances* showed decreases which were not statistically significant.

3. *Coronary Blood Flow Studies:* The data obtained in these studies are presented in table 2.

In this group only there was a significant though slight increase in the *heart rate*. There were no significant changes in the *brachial artery pressure*, the *brachial artery and coronary sinus oxygen contents* and the *brachial artery-coronary sinus oxygen differences*. There were, however, significant increases in *coronary blood flow* and *left ventricular oxygen consumption*, with a significant decrease in the *coronary vascular resistance*. *Myocardial oxygen extraction coefficient (A-V/A)* showed no significant change. There were no significant changes in the arterial levels or percentage extractions of *glucose*, *lactate* and *pyruvate*, but the total left ventricular utilization of these substances increased in parallel with the increase in coronary blood flow. The latter data are not included in the table.

DISCUSSION

The present human studies confirm the previously reported dog findings¹¹ in that Vasoflex produces a significant increase in coronary blood flow, with

little alteration of the heart rate and blood pressure. The increased flow is associated with an increase in the cardiac output, the left ventricular work and the left ventricular oxygen consumption, with no alteration in the coronary sinus blood oxygen content or in the brachial arterial-coronary venous oxygen difference.

The increased availability of oxygen brought about by the enhanced coronary blood flow therefore merely compensates for an increased myocardial demand induced by the drug, rather than exceeding demand, such as would obtain with an "ideal" coronary dilator. In this respect, Vasoflex is similar to aminophylline,⁷ but would appear still to fall short of the beneficial effects of nitroglycerin in dosages which do not critically depress the blood pressure.

It would have been desirable to determine the cardiac output and coronary blood flow concomitantly, in order that mechanical efficiency might be calculated. This was not technically feasible. In comparing the cardiac output, left ventricular work, and left ventricular oxygen uptake data obtained in the two separate groups, however (admittedly not a completely valid comparison), one may infer a decrease in mechanical efficiency of the myocardium.

It would appear to us that, even more than meeting the original criteria set forth by Eckenhoff and associates,⁴⁻⁶ the ultimate value of a drug designed to increase coronary blood flow and myocardial oxygen availability rests upon an actual measurement of myocardial tissue oxygen tension. The lack of change in the coronary sinus oxygen content following administration of Vasoflex suggested that the actual oxygen tension in the myocardium was unaffected. To assess this possibility more directly, the following observations were made in dogs.

In four animals anesthetized with pentobarbital sodium and mechanically ventilated with room air, direct tissue oxygen tensions were measured in that area of the left ventricle supplied by the anterior coronary artery employing a calomel cell electrode and Grass recorder.* Vasoflex, administered intravenously in doses ranging from 0.5 to 1.0 mg./kg. body weight, produced no change in the normally recorded oxygen tension. Following partial occlusion of the artery, the drug did not alter the oxygen tension in either the central or the marginal areas of the ischemic myocardium.

From the foregoing data, therefore, one is forced to conclude that this drug, while inducing a marked increase in coronary blood flow, with only minimal alterations in the heart rate and blood pressure, does not appear to accomplish a positive balance in myocardial oxygen availability. Because of the increased work demand that it produces, it is even conceivable that the drug might aggravate a preexisting myocardial oxygen deficit in subjects with coronary narrowing sufficiently extensive to prevent a vasodilator response.

* These experiments were done in collaboration with Dr. E. Husni, employing a modification of the method of Davies and Brink.⁸

In the past it has not been unusual that a drug showing pharmacologic promise purely as a "coronary vasodilator" has been employed clinically and actually studied objectively at a later date in the laboratory.¹² It would appear wise to employ a generally similar approach to that herein outlined in the case of new drugs currently being developed before releasing them for clinical use and observation.

SUMMARY AND CONCLUSIONS

Vasoflex (N-cinnamyl-methylamino-2-phenylpropane hydrochloride), a synthetic drug related to the catechol amines, produces a marked increase in the coronary blood flow of man when given intravenously. A desirable feature is the lack of any marked alteration in the heart rate and the arterial blood pressure.

The increased coronary blood flow, however, is accompanied by an increased cardiac output, left ventricular work and left ventricular oxygen utilization. Hence the increased flow merely balances, rather than exceeds, an increased myocardial oxygen demand.

It is reemphasized that any drug designed to increase coronary blood flow be investigated as thoroughly as possible by objective laboratory means before attempting a clinical evaluation based on subjective patient response.

ACKNOWLEDGMENT

The authors are indebted for the assistance rendered by Dr. Paul Zingales in some of the experiments.

SUMMARIO IN INTERLINGUA

Vasoflex (marca deponite, Wm. S. Merrell Co.; hydrochloruro N-cinnamyl-methylamino-2-phenylpropanic) es un nove substantia synthetic affin al aminas catecholic. Illo esseva considerate como promittente in le rolo de "dilatator coronari" proque in canes anesthesiate illo habeva augmentate le fluxo coronari de sanguine per usque a 75% sin grados significative de acceleration del frequentia cardiac e de augmento del tension de sanguine.

Quando illo esseva administrate per via intravenose a humanos in doses de 0,5 mg per kg de peso corporee, illo produceva nulle significative alteration del frequentia cardiac, del tension de arteria brachial e pulmonar, del consumption de oxygeno per le corpore total, del differentia arterio-venoso de oxygeno, e del resistentia total pulmonar e systemic. Esseva notate un augmento significative del rendimento cardiac (methodo directe de Fick) e del calculate labor sinistro-ventricular.

Determinationes del fluxo coronari de sanguine (per le methodo a oxydo nitroso) demonstrava un augmento significative del fluxo coronari de sanguine (45%) e un reduction significative del resistentia coronario-vascular. Tamen, isto esseva accompaniate per nulle significative alteration del contento coronari de oxygeno, con le resultato de un augmento de 54% in le consumption myocardial de oxygeno.

Es concludite que Vasoflex de facto produce un augmento marcante del fluxo coronari de sanguine in humanos. Tamen, isto occurre como responsa al augmento del requerimientos de oxygeno del parte del myocardio le qual es inducite per le droga, e le augmentate fluxo coronari es mermante un compensation pro le demanda immediate. Il non es possibile asserer que le droga exerce un effecto benefic quando illo es comparete con nitroglycerina que—a certe nivello critic del tension arterial de sanguine—

augmenta cognoscitamente le fluxo coronari de sanguine sin augmentar le requerimento myocardial de oxygeno.

Es proponite que in tanto que nove pharmacologicamente active "dilatatores coronari" es disveloppate, studios simile al presente es effectuate pro determinar lor ultime valor clinic.

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SPONTANEOUS PNEUMOTHORAX IN APPARENTLY HEALTHY FLYING PERSONNEL *

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SPONTANEOUS pneumothorax at ground level in apparently healthy individuals is relatively innocuous and has a benign course, unless it is complicated by massive collapse of the involved lung, or the development of a tension pneumothorax or hemopneumothorax. In flying personnel, however, the problem is far more serious because of the additional hazards and risks imposed by going to altitude.

The "average" patient who has a spontaneous pneumothorax at ground level usually has a moderate amount of chest discomfort, some dyspnea on effort, and perhaps a cough. He is usually physically able to seek medical advice on his own, and to receive proper care without too much difficulty. In flying personnel, first, there may be an increased frequency of initial pneumothorax due to recurrent exposure to altitude. Second, if the spontaneous pneumothorax should occur at altitude, the already existing problem of hypoxia is greatly magnified. It may be severe enough to result in the abortion of a mission or in an aircraft accident. Similar results might occur with the complications of chest pain, hemorrhage or tension pneumothorax. One case in this series of pneumothorax with pain was associated with syncope. Due to its importance in aviation, an effort is made as a preventive measure to detect those individuals who may be prone to developing a spontaneous pneumothorax. All flying personnel who have had an episode of spontaneous pneumothorax are carefully evaluated in an effort to retain experienced personnel on flying status. Twenty-five individuals among flying personnel who had experienced 38 episodes of spontaneous pneumothorax have recently been studied at the School of Aviation Medicine. These cases were referred after the involved lung had reexpanded.

METHOD AND TECHNICS

Twenty-five individuals with no apparent disorder other than a previous pneumothorax have been studied with a detailed history, a complete physical examination, blood count, hematocrit, erythrocyte sedimentation rate, fasting blood sugar, urinalysis and electrocardiogram. In addition to this

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routine examination, they were studied with pulmonary function tests and a variety of roentgenographic techniques, including routine posteroanterior and lateral chest x-rays, apical lordotic views and apical laminagrams. In 11 of the cases, additional anteroposterior films were taken in the altitude chamber at simulated altitudes of 10,000, 20,000, 30,000, 40,000 and 43,000 feet with pressure breathing. This was accomplished with a Picker 30MA Field X-ray Unit in the altitude chamber, or on the outside of the chamber with exposures taken through an aluminum port.

The pulmonary function tests were primarily ventilatory studies, used to help rule out the presence of disturbed function due to pulmonary pathologic processes. The roentgenographic techniques were also used to detect pulmonary abnormalities, especially air-trapped vesicles or bullae.

RESULTS

Of the 25 individuals, all of whom were flying personnel, only three (12%) had had their episodes of spontaneous pneumothorax while in flight. These three individuals had had a total of 11 pneumothoraces, all at altitude, either in an aircraft or in the altitude chamber. In one of these individuals (case 11), the first two episodes occurred in flight and the subsequent four episodes occurred in the altitude chamber during diagnostic studies. These 11 pneumothoraces constituted 29% of the total number of episodes. Thirty-seven per cent of the episodes occurred while the individual was at rest. Twenty-three per cent were associated with some type of physical activity. A paroxysm of coughing preceded 8% of the pneumothoraces. In one case (2%), the particular physical state of the individual prior to the episode was not remembered.

Of the total 25 cases, 12 (48%) had right-sided involvement. An equal number had left-sided involvement, and one case presented a history of alternate involvement of the right and left sides.

Following re-expansion of the involved lung, pulmonary function tests of ventilation were within normal limits in all 25 cases. The routine posteroanterior and lateral chest x-rays disclosed pathologic entities (cysts, emphysematous bullae or pleural blebs) which would account for the spontaneous pneumothorax in seven of the cases (28%). In an additional seven cases (28%), apical laminagraphy revealed the pathologic etiology.

In 11 cases, x-ray studies were performed in the altitude chamber. In six of these cases, where the routine x-ray studies were unremarkable, the chamber films were of no additional help. In one of the patients (case 11), however, the films taken at various altitudes demonstrated the presence of an expanding bulla in the left apex and a very small, limited pneumothorax. These findings were not demonstrable on the routine roentgenographic studies, except in retrospect. In the four remaining cases, where the pulmonary pathologic process resulting in the pneumothorax had been demonstrated by routine x-ray studies, the altitude chamber films disclosed that

these were air-containing cavities which expanded with increasing altitude (decreasing atmospheric pressure). Thus, the altitude chamber was of help in diagnosis in only one case of this series (case 11). All other cases were diagnosed by other x-ray technics.

DISCUSSION

The true incidence of spontaneous pneumothorax in an apparently healthy population is unknown. Heath¹ surveyed some 28,000 admissions to an Air Force Hospital and found only 10 cases. It has been reported in almost every age group, including the newborn,² but it is primarily a disease of youth. In Myers³ series of 115 cases, 92% were below the age of 40 years at the time of the first diagnosed attack, and 75% were between the ages of 20 and 35 years. The age range of this series is 20 to 49 years, with an average of 27.9 years and a mode of 26.3 years. The population from which this series was drawn is primarily a youthful one, and it would be expected that the age at which the first diagnosed incident occurred would be somewhat younger than that of the general population. However, the figures do correlate well with most series.^{3, 4}

Apparently, spontaneous pneumothorax is a relatively rare occurrence at altitude. Heath¹ records only one episode in 86,916 man flights in the altitude chamber. Explosive or sudden decompression was not performed on these flights. In a series of 771 explosive decompressions, he has not noted a single episode. At the School of Aviation Medicine over the last five years there have been approximately 10,000 man flights in the altitude chamber; 4,000 of these man flights included a rapid decompression (95% of which were from 8,000 to 22,000 feet). In this series there were only two suspected cases of spontaneous pneumothorax, but neither was confirmed by diagnostic study.

In Leach's series⁵ of 126 cases of spontaneous pneumothorax occurring in young adult males, 41 were flying personnel. There was not one episode of pneumothorax occurring in aerial flight. Of the total 129 episodes occurring in the 126 cases, it was suspected that three episodes might have been related to an altitude chamber flight. Markovits and Phillips⁶ reported a case of spontaneous pneumothorax during a pull-out from a power dive in aerial flight.

In this series of 25 cases with 38 episodes (table 1), there were three cases (cases 1, 2, 11) and seven episodes occurring in aerial flight. One of these (case 11) also had four subsequent episodes in the altitude chamber, recognized in retrospect, during his diagnostic studies.

The true incidence of spontaneous pneumothorax occurring in aerial flight is unknown. If it is as infrequent as most studies have shown it is indeed fortunate, because of the severity of the problem and its complications. In this series, the seven episodes of pneumothorax in aerial flight occurred in two pilots and one navigator. In each case, each episode was severe

enough to incapacitate the individual and cause him to relinquish his duties. The aircraft then descended to lower altitude and the mission was aborted. At lower altitudes, and breathing 100% oxygen, these individuals were fairly comfortable, except for the associated chest pain. The increase in atmospheric pressure associated with decrease in altitude and the supplementary supply of oxygen was apparently of sufficient quantity to correct the hypoxia resulting from the sudden decrease in vital capacity and the higher altitudes. The associated chest pain was a prominent feature in a majority of the episodes. If any one of these episodes had occurred in a single-seated aircraft (high performance or otherwise), it can easily be seen how it could have resulted in death and destruction, and the case filed as an "unexplained aircraft accident."

TABLE 1

| Case Number | Age at Time of Episode | Side Involved | Incident Associated with Pneumothorax | Findings on Investigative Procedures |
|-------------|--|--------------------------------------|--|---|
| 1 | 30 yrs. | Left | In aerial flight | PA chest film: solitary vesicle in the left lower lobe.* |
| | 30 yrs. | Left | In aerial flight | |
| | 30 yrs. | Left | In aerial flight | |
| | 31 yrs. | Left | In aerial flight | |
| 2 | 34 yrs. | Right | In aerial flight | PA and laminagrams: bilateral apical vesicles. PA films in altitude chamber: expansion of vesicles with increasing altitude. |
| 3 | 33 yrs. | Right | Seated: following judo training and flying | PA and laminagrams: vesicles in right apex. PA films in altitude chamber: expansion of vesicles with increasing altitude.* |
| 4 | 23 yrs. 24 yrs. 24 yrs. | Right Left Right | Seated Seated Coughing | PA chest film suggested bilateral apical vesicles which were later confirmed by laminagrams.* |
| 5 | 27 yrs. | Right | Seated | No findings. |
| 6 | 26 yrs. | Right | Climbing stairs | Laminagrams: vesicles in right upper lobe.* |
| 7 | 22 yrs. 23 yrs. | Left Left | Sleeping Cleaning car | PA, lateral and laminagrams: bilateral apical pleural thickening. Altitude chamber films not accomplished. |
| 8 | 20 yrs. | Left | Walking | Apical laminagrams: bilateral vesicle formation. |
| 9 | 20 yrs. | Left | Sleeping | No findings. |
| 10 | 33 yrs. | Right | Sleeping, following golf and horseback riding | No findings. |
| 11 | 27 yrs. 31 yrs. 31 yrs. 33 yrs. 33 yrs. 33 yrs. | Left Left Left Left Left | In aerial flight In aerial flight with sudden decompression Chamber flight Chamber flight Chamber flight Chamber flight | Altitude chamber films revealed a spontaneous pneumothorax which increased with altitude. Subsequent apical laminagrams revealed pleural thickening and emphysematous vesicles in the left apex. |

TABLE 1—(Continued)

| Case Number | Age at Time of Episode | Side Involved | Incident Associated with Pneumothorax | Findings on Investigative Procedures |
|-------------|------------------------|----------------|---------------------------------------|--|
| 12 | ? | Left | ? | No findings. Altitude chamber films not done. |
| 13 | 38 yrs. | Left | Walking | Apical laminagrams: vesicles in left apex, and bilateral apical pleural thickening.* |
| 14 | 23 yrs. | Right | Preflighting Aircraft | No findings. |
| 15 | 31 yrs. | Left | Playing football | Laminagrams: solitary cyst in left lower lobe. |
| 16 | 49 yrs. | Right | Sitting | Apical laminagrams: pleural vesicles at apex of right lung. Altitude chamber films: vesicles at both apices which expand with increasing altitude. |
| 17 | 23 yrs. | Left | Sleeping | No findings. |
| 18 | 24 yrs. | Right | Coughing | No findings. |
| 19 | 33 yrs. 38 yrs. | Right Right | Sitting Standing | PA chest film: vesicles right apex. |
| 20 | 22 yrs. | Right | Seated | No findings. |
| 21 | 23 yrs. | Right | Coughing | No findings. |
| 22 | 27 yrs. 28 yrs. | Left Left | Carrying packages standing | Apical laminagrams: bilateral pleural vesicles. |
| 23 | 29 yrs. | Right | ? | PA chest film: bilateral apical vesicles. |
| 24 | 23 yrs. 25 yrs. | Left Left | Playing golf Driving car | Only routine PA and lateral films performed, which were unremarkable. |
| 25 | 30 yrs. | Left | Sitting | Only routine PA chest film performed, which was unremarkable. Altitude chamber flight was normal, but x-rays were not taken. |

* These cases were operated upon, and had excisional surgery and/or parietal pleurectomy.

Of the remaining 27 episodes of pneumothorax occurring at ground level, 14 were associated with little or no physical effort, one with a moderate amount of activity, and three with paroxysms of coughing; in one the activity was unknown. These figures correspond to those reported in 1927 by Friesdorf⁷ who, in reviewing 177 cases of pneumothorax from the literature, found 40% associated with "considerable exertion," 40% with "slight exertion" and 20% with "trivial movement." The activity at the time of the episode in Leach's⁵ series was 39% at rest, 30% associated with mild activity, and 10% with extreme activity; in 20% the activity was unknown. It is apparent that physical effort is unrelated to the frequency of occurrence of spontaneous pneumothorax in apparently healthy individuals. If it were, one would expect an increased frequency in strenuous manual laborers, but this was not found in the series of Perry⁴ or Kjaergaard.⁸

In the 25 cases of pneumothorax, the incidence of right and left lung involvement was equal. In one (case 4) there was bilateral but not simultaneous involvement. Perry⁴ also found equal involvement of the right and the left lung in his group of 85 apparently healthy individuals. In the larger series of Leach⁵ the right side was involved in 60% of the cases. There is no apparent predominance of one side over the other.

The etiology of spontaneous pneumothorax in the apparently healthy individual still remains in some doubt because of our inability to demonstrate abnormalities clinically prior to postmortem examination in all cases. In 1884 West⁶ demonstrated at post mortem that the normal, healthy pleura could not be ruptured *in situ* with pressures of less than 200 mm. of mercury. He pointed out that an intrapulmonic pressure of this magnitude could never be achieved during life, and that therefore pleural rupture was dependent upon some pathologic condition which weakened it.

In the apparently healthy individual there are four pathologic entities which must be considered as the etiology of spontaneous pneumothorax:

1. Pleural adhesions.
2. Congenital cysts of the lung.
3. Scar tissue vesicle.
4. Emphysematous valve vesicle.

Pleural adhesions are reported to cause the formation of subpleural vesicles at the point of their insertion into the visceral pleura.⁴ Autopsy reports by Pitt,¹⁰ Housden and Piggot¹¹ and Gough¹² demonstrated that during severe respiratory effort, such as coughing, the adhesions pull on the lung and tear these vesicles. Of the 14 cases of spontaneous pneumothorax with demonstrable pathologic conditions in this series, there was one case with bilateral pleural adhesions alone, and two cases associated with bullae or blebs. Ruptured pleural adhesions are probably an infrequent cause of spontaneous pneumothorax.

Congenital cystic disease of the lungs is also a rather rare cause of spontaneous pneumothorax in apparently healthy individuals. Its presence in the newborn is a well recognized cause of pneumothorax. The incidence of such cysts is greatest in patients of less than five years of age, and progressively decreases with increasing age. They may be solitary or multiple in number, and may be localized or scattered throughout the lung. In addition, they may or may not be associated with other congenital abnormalities. Of the five cases in this series who underwent an operative procedure, a pathologic diagnosis of congenital cysts of the lung was established in only one (case 3).

Orth,¹³ Hayashi¹⁴ and Fischer¹⁵ described the formation of scar tissue vesicles developing especially in the apices of the lungs through atrophy and inflation, resulting from the presence of some valvelike structure at the base of the vesicles. These valvelike structures develop as a result of a small,

localized inflammatory process, with subsequent scar tissue formation producing a constriction of the bronchioles. Atrophy and deformity of the adjacent pulmonary tissue are a result of the shrinking scar. These valves allow air to pass freely into the vesicles but prevent its egress. This results in progressive distention, eventual rupture and pneumothorax.

Kjaergaard⁸ in 1932 reported five of his own cases and reviewed six autopsied cases from the literature where the cause of pneumothorax was found to be rupture of a solitary vesicle at the apex of the lung, with or without scar tissue. Some three years later he reported upon three additional autopsied cases whose lungs contained these valvular vesicles. Two were due to scar tissue, and the one without scar tissue was considered to be due to bullous emphysema.

Emphysematous valve vesicles develop through local emphysematous change without scar tissue. It is a frequent residual of many pathologic conditions in the lung. They may occur as large solitary vesicles on the lung borders. Many cases are reported in the literature⁴ where thoracoscopy of apparently healthy patients with spontaneous pneumothorax revealed numerous emphysematous bullae. Generalized emphysema in young people is a relatively rare condition. Its occurrence is usually preceded by a long-standing history of asthma. Localized emphysema, however, is found in all age groups and is asymptomatic. The rupture of this type of vesicle is probably the most important cause of benign spontaneous pneumothorax. Kjaergaard⁸ suggested that the infrequency of spontaneous pneumothorax in patients with generalized emphysema was due to the fact that emphysematous bullae in generalized emphysema are rarely valve vesicles, and usually communicate freely with other air passages.

Our small series of cases tend to confirm the impression that all cases of spontaneous pneumothorax have some basic underlying pathology. By far the most frequent pathologic finding with roentgenographic technics was air-containing vesicles and cysts. In every case where the vesicles or cysts were exposed to increasing altitudes, it was of great interest to note their expansion with the progressive decrease in atmospheric pressure. This observation confirms the impression that such vesicles and cysts are air-containing sacs which may permit the entrance of air, but certainly prevent its egress. It can readily be seen how such cysts and vesicles could rupture with sudden increases in the intravesicle pressure such as might occur with paroxysms of coughing or a rapid decompression.

The clinical terminology utilized to describe vesicle formation in the lungs is somewhat confusing. In 1927 Miller¹⁰ described the difference between blebs and bullae. Blebs are caused by the rupture of pulmonary alveoli immediately adjacent to the visceral pleura. This allows air to escape into the pleura and separates it from the underlying alveoli, forming a thin-walled cavity outside the lung itself. Bullae, however, occur within the parenchyma of the lung by overdistention, rupture and coalescence of alveoli.

They may protrude beyond the surface of the lung, but they are covered by intact alveoli.

Of the five cases that were operated upon in this series, the pathologic specimens revealed emphysematous vesicles in four and congenital cystic disease in one. This is in agreement with the observations of Kjaergaard that emphysematous vesicles are the most frequent cause of benign spontaneous pneumothorax.

Although only 11 of the total of 25 cases showed evidence of a pathologic process in the roentgenographic studies, and only six of these had bilateral involvement, it is felt that emphysematous and scar tissue vesicles usually occur bilaterally. Because of their microscopic size we are unable to demonstrate them clinically with present technics. It is interesting to note that in this group of 25 patients the initial symptomatology was not severely incapacitating in the 22 cases that occurred at ground level. However, each of the episodes which occurred during aerial flight in the three remaining cases was of sufficient severity to incapacitate the individual and cause him to relinquish his duties. This is not always true, as noted in another case of reported pneumothorax⁶ occurring during flight.

Although the physical signs and laboratory studies used to confirm the suspected diagnosis of pneumothorax are well known, it is perhaps worth repeating the importance of obtaining posteroanterior roentgenograms of the chest in expiration when the diagnosis cannot readily be made with the inspiratory film alone. In expiration, the less aerated lung is denser and is more easily differentiated from the small pneumothorax.

The therapy of small, benign, uncomplicated spontaneous pneumothorax is primarily bed-rest. Myers⁸ found that in 102 of his 115 cases of spontaneous pneumothorax, adequate therapy was: none in 41 cases, bed-rest of less than one week's duration in 26 cases, and bed-rest of less than three weeks' duration in 35. In this series of 25 cases, therapy was carried out by a variety of different physicians and undoubtedly reflects differences in their training. Five cases required no treatment of any kind. Thirteen required bed-rest of less than three weeks' duration. Six were treated with aspiration, and one case required the insertion of a tube with water-seal drainage after failure of the lung to reexpand on bed-rest alone. More complicated cases—for example, large pneumothoraces or complication of atelectasis or hemorrhage—require other therapeutic and diagnostic consideration.

The reported incidence of recurrence of spontaneous pneumothorax in flying personnel and the general population varies. In Kjaergaard's⁸ series of 51 patients there was a 20% recurrence rate. In 1931 Wood¹⁷ found a 21% recurrence rate in 71 patients. Of 100 patients followed for from one to 29 years, Myers⁸ found that 29 (29%) had a recurrence. The lowest reported recurrence rate was 4.7% in Perry's⁴ series. If there is a recur-

rence, in the great majority of instances it will occur within one year of the initial attack.^{4, 8}

Up to the present time, five cases in the series have undergone a corrective surgical procedure. One (case 1) had a local resection of the single cyst. The four other patients had segmental or wedge resections of the involved area and a parietal pleurectomy. One of the four (case 4) had this procedure performed on both sides. All four were returned to flying status after full recovery and complete physical and laboratory evaluation. This included pulmonary function studies and an altitude chamber ride to 43,000 feet, with chest x-rays and a rapid decompression from 8,000 to 22,000 feet.

The primary concern at altitude in flying personnel who have a spontaneous pneumothorax is the possibility of complete collapse of the involved lung and/or the development of a tension pneumothorax. Either complication could severely compromise the ventilatory function of the remaining lung and could embarrass cardiovascular hemodynamics. This would increase in severity the problems of hypoxia and circulatory adjustments associated with flying. Corrective surgery in the form of segmental or wedge resection of the diseased area and parietal pleurectomy will minimize the possibility of a recurrence and the previously mentioned complications. If a spontaneous pneumothorax should recur, it would be localized and the lung would never undergo massive collapse because of the firm, fibrous adhesions between the pleura and the thoracic wall.

Unfortunately, this procedure does not solve the problem of hemo-pneumothorax due to tearing of adhesions, nor does it prevent the development of mediastinal emphysema. Rupture of alveolar walls may result in the escape of air into the surrounding connective tissue and dissect along fascial planes towards the mediastinum or towards the visceral pleura. If the air goes to the pleura, it may produce a pleural bleb or rupture, and result in a spontaneous pneumothorax. Air reaches the hilar structures via the sheaths of the arteries; it spreads out in the mediastinum and dissects into the soft tissues of the anterior chest wall and the neck.¹⁸ It is indeed fortunate that these complications are rather infrequent.

A pneumothorax occurring at ground level will expand on exposure to altitude and may cause the complications mentioned above. Actually, an unrecognized pneumothorax occurring at ground level, with its expansion at subsequent altitude exposure, is more apt to cause mediastinal shift and other complications due to gaseous expansion. The intrathoracic pressure of pneumothorax occurring at altitude will diminish after descent to ground level.

CASE REPORTS

Case 1. In early 1953, while flying a high altitude training mission, a 31 year old navigator found that his aircraft had caught fire. He helped to put out the fire, then with the termination of the excitement noted a severe left-sided chest pain; this

was increased in severity with motion and deep breathing. The aircraft descended to lower altitudes and the patient's symptomatology decreased. The mission was terminated but his chest pain remained and lasted some three days at ground level. He had two similar recurrences in aerial flight during the remainder of that year but failed to report to the flight surgeon.

In 1954, while returning from a high altitude mission, the aircraft commander found it necessary to fluctuate the cabin pressure between 10,000 and 18,000 feet. At the termination of the flight the patient noted severe left-sided chest pain, dyspnea and weakness. The chest pain was increased with motion and deep breathing. Upon landing, the patient was immediately hospitalized. A routine posteroanterior chest x-ray confirmed the diagnosis of spontaneous pneumothorax. Upon reexpansion of the lung a solitary vesicle was noted in the left lower lobe of the lung on the routine chest film. The vesicle was subsequently excised and the pathologic report was "emphysematous bleb." Follow-up studies, including pulmonary function tests, were unremarkable. An altitude chamber flight was scheduled to qualify him again for flying, but this was not completed because the patient lacked adequate motivation for return to flying status.

Case 2. A 34 year old pilot experienced right-sided chest pain while flying at high altitude. The pain was sudden in onset, associated with dyspnea, and increased with motion and deep respiration. He relinquished the controls of the aircraft to his co-pilot and the mission was aborted. Upon descent to lower altitudes the severity of the symptoms decreased, but the pain and dyspnea persisted for a number of days at ground level.

On his subsequent annual physical examination, a routine chest film disclosed bilateral apical vesicles. This finding was confirmed by apical laminagraphy. X-ray films in the altitude chamber showed the expansion of these vesicles with increasing altitude. Pulmonary function studies were normal.

*Case 11.** A 34 year old observer first experienced chest pain in 1948 while flying at 17,000 feet. The pain was sudden in onset, maximal in the second and third intercostal spaces anteriorly, and increased by respiration; it radiated downward and backward, was accompanied by dyspnea, and caused him to relinquish his duties. Upon descent to lower altitudes the pain diminished. For three to four days after return to ground level he noted a vague discomfort in his left shoulder.

The patient remained asymptomatic until 1952, at which time a sudden decompression of his aircraft to 22,000 feet resulted in a recurrence of the previously described symptomatology, and again he had to discontinue his activities as a navigator. Upon landing he was examined by a flight surgeon and no abnormalities were noted. Subsequent studies, including chest x-ray, routine electrocardiogram, Master's exercise tolerance test and an upper gastrointestinal series, were also normal. An altitude chamber flight again resulted in chest pain at 15,000 feet, but further investigation was prevented when the patient was transferred to another base.

The patient continued on flying status without difficulty until January, 1955. At that time a routine refresher chamber flight resulted in a similar episode of chest pain. Routine investigative studies were again unremarkable. Thereafter the patient underwent a series of medical evaluations, including chamber flights to various altitudes, with and without explosive decompression. On every occasion he had a recurrence of his chest pain. Prior to and following some of these chamber rides, chest x-rays were performed. On some of the postflight chest films a small area at the apex of the left lung appeared to indicate a pneumothorax.

* This case was studied and previously reported in detail by Amdur, R. A.: Recurrent spontaneous pneumothorax caused by aerial flight: report of a case, *J. Aviation Med.* 27: 456, 1956. It is reviewed here because of its significance in the diagnostic problem of pneumothorax.

The patient was referred to the School of Aviation Medicine for consultation. Physical examination, routine laboratory studies and pulmonary function tests were within normal limits. A diagnostic altitude chamber flight with chest x-rays at various altitudes was performed. At 15,000 feet the patient experienced chest pain which increased in severity as the altitude chamber ascended to 30,000 feet. Upon descent the chest pain lessened, until it was a dull ache at ground level. A review of the chest x-rays revealed the presence of a small but definite pneumothorax on the film taken at 20,000 feet. With increasing altitude the pneumothorax was seen to expand and on descent to decrease in size. A chest film taken 24 hours after the flight revealed almost complete reabsorption of the pneumothorax. Subsequent laminographic studies revealed the presence of emphysematous vesicles and pleural thickening in the left apex.

Case 4. A 25 year old pilot in 1956 had had the sudden onset of right chest pain while seated. He visited the flight surgeon the following day, and a diagnosis of spontaneous pneumothorax of the right lung was made clinically and confirmed by x-ray. The patient was hospitalized and treated with aspiration of the pleural space and bed-rest. Recovery was uneventful and he was returned to flying status when his routine laboratory studies did not demonstrate evidence of disease.

In January, 1957, while seated, the patient experienced another episode of chest pain, this time involving the left side. Suspecting the diagnosis, he visited his flight surgeon immediately and was hospitalized with the diagnosis of spontaneous pneumothorax of the left lung. Treatment was aspiration and bed-rest. The 14-day hospital course was uneventful, and routine diagnostic studies were unremarkable. The patient was removed from flying status.

In February, 1957, the patient had his third episode of pneumothorax, again involving the right lung. His hospitalization was 14 days and completely benign.

In September, 1957, the patient was evaluated at a major Air Force medical center. Routine roentgenograms of the chest suggested bilateral, apical vesicle formation. Laminagrams confirmed these findings. Preoperative pulmonary function studies were normal. The patient underwent an operative wedge resection of the right apex and a parietal pleurectomy. A similar procedure was performed on the left side some six weeks later. Pathologic examination of both specimens revealed localized emphysematous vesicles. The patient's postoperative course was unremarkable, and his pulmonary function tests were within normal range.

Five months later, complete evaluation at the School of Aviation Medicine was unremarkable. This included physical examination, routine laboratory studies and pulmonary function tests. Routine chest films, laminagrams and films in the altitude chamber revealed only the residuals of the operative procedures. There was no evidence of vesicles. The altitude chamber ride to 43,000 feet with pressure breathing and a rapid decompression from 8,000 to 22,000 feet was uneventful.

SUMMARY AND CONCLUSIONS

Although spontaneous pneumothorax can usually be considered lightly when it occurs at ground level, its occurrence in aviation may result in the abortion of a mission, a serious accident or a major disaster. A better understanding of the etiologies, precipitating causes, complications, likelihood of recurrences and treatment may lead to the prevention of accidents resulting from spontaneous pneumothorax and the retention on flying status of trained personnel.

This report is both an analysis of 38 episodes of spontaneous pneumo-

thorax occurring in 25 apparently healthy flying personnel and a brief review of the literature. The presented cases have been studied extensively with routine and specialized technics, including pulmonary function studies and chest roentgenograms in the altitude chamber.

In the three cases of this series, spontaneous pneumothorax occurring in aerial flight was disabling because of the pain, and the dyspnea resulting from the altered ventilatory function of the lung and the already existing problem of hypoxia at altitude.

The possible etiologies of spontaneous pneumothorax are reviewed and the following entities are considered:

1. Pleural adhesions.
2. Congenital cysts of the lung.
3. Scar tissue vesicles.
4. Emphysematous valve vesicles.

It is suggested that these entities are usually bilateral in occurrence. The impression that congenital cysts, scar tissue vesicles and emphysematous valve vesicles are air-trapped sacs is given further credence by x-ray studies in the altitude chamber.

The incidence and recurrence rates in the literature are reviewed. Diagnostic technics, operative procedures and evaluation studies are discussed from the point of view of continuing a useful flying career.

SUMMARIO IN INTERLINGUA

Iste reporto presenta un revista del problema de pneumothorace spontanee, con attention special prestate a su relation al aviari. Es reportate 38 episodios de pneumothorace spontanee occurrente in 25 apparentemente san subjectos del personal aviatori. Pneumothorace representa un hasardo additional al aviator in ascender a grande altitude. Pneumothorace occurrente in volo magnifica possibilmente le problema del hypoxia. Sever dolores in pneumothorace in volo pote causar syncope. Un episodio de syncope con pneumothorace es reportate.

In tres del casos del presente serie, pneumothorace occurreva in volo, accompaniate de invalidante dolor e dyspnea.

Le casos hic presentate esseva studiate extensemte, incluse le uso de tests del function pulmonar e roentgenogrammas thoracic in le camera de altitude.

Le etiologias possibile de pneumothorace spontanee es passate in revista. Le sequente entitates es considerate: (1) Adhesiones pleural. (2) Congenite cystes pulmonar. (3) Vesiculas de histos cicatrisante. (4) Emphysematose vesiculos valvular.

Es postulate que iste entitates es usualmente bilateral. Le impression que cystes congenite, vesiculas de histo cicatrisante, e vesiculas valvular emphysematose es saccos de aere intrappate es corroborate per studios roentgenographic in le camera de altitude. Iste studios demonstrava le expansion del aere intrappate con crescente altitudes e le reduction de su dimensiones con le retorno al pression del nivello del superficie del terra.

Es summarisate le datos trovate in le litteratura con respecto al incidentia e al frequentia de recurrentias de pneumothorace spontanee. Technicas diagnostic, mesuras

chirurgic, e studios evalutatori es discutite ab le punto de vista del aviador qui desira persistier in su carriera.

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LEUKEMIA AND TUBERCULOSIS *

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PROBABLY the most important question still not resolved in the literature of leukemia is that concerning the relation of the disease to infection. Infection may stimulate blood changes which would be regarded as leukemic by all but the most cautious of hematologists. It has also been noted that infection can cause the leukemic blood and marrow pictures to revert almost to normal. There is no proof, however, that infection can either give rise to or cure true leukemia.

The infection about which most has been written concerning its relation to leukemia is undoubtedly tuberculosis. As late as 1956 Rosenthal,¹ in a comprehensive review of the subject, was able to say that the prevalence of the association of the two diseases was unknown. This study was undertaken to answer the question, Does tuberculosis occur more commonly in association with leukemia than in the general group of diseases reaching the postmortem room?

In the past, large numbers of reports have accumulated of single cases and small collections of cases where the two diseases coexisted, but few reports of controlled series have been forthcoming. One such survey, however, was that of Susman,² published in 1903. This author reviewed the postmortem reports of four large London hospitals, finding 41 cases of leukemia and 877 of tuberculosis in 7,200 necropsies. This gave an overall tuberculosis incidence of 12.2%, and as the incidence of tuberculosis in his 41 cases of leukemia was 2.4% (one case), the observed difference was therefore statistically significant. Parker et al.³ reported the occurrence of tuberculosis in 10% of 81 cases of leukemia, and the general hospital incidence was stated to coincide. Wintrobe and Hasenbush⁴ found no tuberculosis in 86 cases of leukemia. Kirshbaum and Preuss⁵ reported the occurrence of tuberculosis in 13% of 128 cases of leukemia. No information as to what constituted "tuberculosis" was given, but the authors concluded that 13% was not unusual considering the local incidence. More recently, interest in this question has revived, and Abbat and Lea,⁶ in a statistical treatment of cases of leukemia found in the Armed Forces of the United Kingdom, concluded that tuberculosis did not occur more commonly in leukemia than would be expected.

For the purposes of this survey, it was decided that, for a case to be

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accepted as leukemia, both massive cellularity and anaplasia of the marrow and leukemic infiltration of the viscera must be present.

MATERIAL

Full reports on postmortem examinations have been collected in Glasgow at the Royal and Western Infirmarys since 1925, at the Royal Hospital for Sick Children since 1926, and at the Victoria Infirmary since 1947. Since 1949, the Pathology Department at the Royal Infirmary has conducted post-mortem examinations for the following hospitals: Eastern District, Canniesburn and Belvidere Hospitals in Glasgow, and also Gartloch, Strathclyde and Stonehouse Hospitals in Lanarkshire. Thus, almost all of the post-mortem material with available histology obtainable in the West of Scotland between the years 1925 and 1952 has been reviewed.

The records of these departments have been examined, and all cases of tuberculosis and of leukemia have been noted and studied.

RESULTS

The crude results are shown in table 1, from which the following figures can be extracted for comparison:

Total tuberculosis as percentage of total postmortem reports: 6.5%.

Total tuberculosis with leukemia as a percentage of total leukemias: 5.6%.

TABLE 1
Figures Extracted from Records of Post Mortems

| | Total Postmortem Reports | Total Cases of Tuberculosis | Total Cases of Leukemia | Cases Showing Leukemia and Tuberculosis |
|---------------------|--------------------------|-----------------------------|-------------------------|---|
| General Hospitals | 20,331 | 930 (4.6%) | 238 (1.2%) | 15 |
| Children's Hospital | 6,773 | 833 (12.5%) | 47 (0.7%) | 1 |
| Total | 27,104 | 1,763 (6.5%) | 285 (1.05%) | 16 |

The difference is not statistically significant.

It is notable that in the Royal Hospital for Sick Children the incidence of tuberculosis is much higher than in the other hospitals (12.5% as against 4.5%). If there had been a causal connection between tuberculosis and leukemia, it might have been expected that more cases of leukemia would have been found there. But, although the incidence of tuberculosis is three times that of the other hospitals, the incidence of leukemia is only 0.7%, as against 1.2% in the other hospitals.

The results of this survey show statistically that tuberculosis occurs no more often in association with leukemia than in the entire group under consideration. As some previous reports have diminished their own usefulness

TABLE 2
Details of the Tuberculous Lesions Found in Those Cases Where the Disease Was Associated with Leukemia

| | |
|----------------|--|
| <i>Case 1</i> | Chronic myeloid leukemia; miliary tubercles in peritoneum; caseation in liver and spleen; tubercle bacilli recovered from inguinal glands and peritoneal fluid |
| <i>Case 2</i> | Chronic lymphatic leukemia; single caseous focus in right upper lobe |
| <i>Case 3</i> | Chronic myeloid leukemia; one large caseating mesenteric gland |
| <i>Case 4</i> | Acute lymphatic leukemia; right apical fibroid tuberculosis with central caseation |
| <i>Case 5</i> | Chronic lymphatic leukemia; old healed pulmonary tuberculosis with central calcification |
| <i>Case 6</i> | Chronic lymphatic leukemia; consolidated right upper zone with apical adhesions and fibrinous exudate (included as no histology available) |
| <i>Case 7</i> | Acute lymphatic leukemia; one caseous paratracheal gland |
| <i>Case 8</i> | Acute lymphatic leukemia; left apical miliary tubercles with one cased mediastinal gland; primary focus in left lower lobe (age, 11 years) |
| <i>Case 9</i> | Chronic myeloid leukemia; two caseating lumbar glands |
| <i>Case 10</i> | Chronic myeloid leukemia; cased tubercles in lungs; early tubercles in related lymphatics |
| <i>Case 11</i> | Chronic myeloid leukemia; tuberculous focus in left upper lobe; one cased mediastinal gland |
| <i>Case 12</i> | Monocytic leukemia (Nägeli); several acute caseating lesions at right apex |
| <i>Case 13</i> | Acute myeloid leukemia; primary tubercles in right upper lobe; caseous tracheobronchial and paratracheal glands (age, 13 years) |
| <i>Case 14</i> | Acute lymphatic leukemia; fibrocaseous glands in left lung; healed primary lesions in left upper lobe (age, two years) |
| <i>Case 15</i> | Chronic myeloid leukemia; tuberculous peritonitis with scattered tubercles in bowel and spleen; cased abdominal glands |
| <i>Case 16</i> | Acute myeloid leukemia; cased Ghon focus with local lymphatic spread; a few miliary tubercles in spleen (age, three years) |

by failing to indicate the site and severity of the tuberculous lesions found, this information is presented in extenso in table 2. It is admitted that, unless a special, previously planned search is made at the time of postmortem examination, it cannot be said with certainty that no tuberculous focus exists in any part of the body. This objection, however, applies equally to the whole group under consideration and, although some small tuberculous foci may have passed unrecorded, the statistical conclusion is still valid.

TABLE 3
Incidences of Tuberculosis and of Leukemia Between the Years 1925 and 1952

| | Total Postmortem Reports | Total Cases of Tuberculosis | Total Cases of Leukemia |
|---------|--------------------------|-----------------------------|-------------------------|
| 1925-28 | 3,245 | 190 (5.9%) | 20 (0.62%) |
| 1929-32 | 3,664 | 232 (6.3%) | 20 (0.55%) |
| 1933-36 | 3,793 | 220 (5.8%) | 42 (1.11%) |
| 1937-40 | 3,972 | 280 (7.1%) | 34 (0.86%) |
| 1941-44 | 3,399 | 281 (8.3%) | 38 (1.12%) |
| 1945-48 | 3,843 | 326 (8.5%) | 52 (1.35%) |
| 1949-52 | 5,188 | 234 (4.5%) | 79 (1.52%) |

Chi-square = 41.3; n = 6; p = 0.01 for leukemia incidence.

In table 3 the present series is shown, divided into four-year groups to show the changing incidences of tuberculosis and leukemia.

There is clearly an increase in the incidence of leukemia similar to that noted in Scotland by Gauld et al.⁷ The statistical analysis shows that the chances of the increase being fortuitous are one in 100. The incidence of leukemia runs counter to the changes in the tuberculosis rate.

Susman² believed that when leukemia and tuberculosis coexisted, the association was two and one-half times more likely to be with lymphatic than with myeloid leukemia. This is far from being the case in the present series, in which the association was twice as frequent with myeloid as with lymphatic leukemia (table 4).

TABLE 4
The Classification of Cases by Cell Type

| | No. of Cases | Cases of Leukemia and Tuberculosis |
|-------------------|--------------|------------------------------------|
| Acute myeloid | 68 (23.9%) | 2 |
| Chronic myeloid | 63 (22.1%) | 8 |
| Acute lymphatic | 75 (26.3%) | 3 |
| Chronic lymphatic | 43 (15.1%) | 2 |
| Monocytic | 17 (6.0%) | 1 |
| Unclassified | 19 (6.6%) | 0 |

SUMMARY AND CONCLUSIONS

1. Postmortem reports of 27,104 cases were reviewed, and tuberculosis was found in 6.5%. Tuberculosis was found in 5.6% of 285 postmortem reports on cases of leukemia.

2. It is concluded that tuberculosis occurs infrequently in association with leukemia, and no more often with leukemia than in postmortem material generally.

3. The incidence of leukemia was found to be increasing, and the cell-type percentages were noted.

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SUMMARIO IN INTERLINGUA

Il existe un forte impression clinic que leucemia e tuberculose coexiste plus frequentemente que es explicabile per coincidentia. Grande numeros de reportos de casos individual o de micre grupplos de casos se trova in le litteratura sed nulle reporto de un controlate serie de casos private. Le presente articulo se occupa del question: Es le association del duo conditiones plus frequente que lo que on expectarea como efecto del coincidentia?

In un total de 27.104 reportos de necropsias colligite in le departimentos de pathologia de 10 major hospitales in Scotia occidental inter 1925 e 1952, le autor trovava 1.763 casos de tuberculose, 283 casos de leucemia, e 16 casos in que le duo morbos esseva coexistente. Assi le incidentia general de tuberculose esseva 6,5% e le

incidentia de tuberculose in leucemia 5,6%. Le differentia non es significativa. Le criterios requirite pro un diagnose de leucemia esseva (1) massive cellularitate e anaplasia del medulla e (2) infiltration leucemic del visceres.

Le incidentia de leucemia in Scotia inter 1925 e 1952 se revelava como de magnitude crescente. Iste mesme facto ha essite describite per altere autores. Esseva notate que tuberculose coexisteva con leucemia myeloide duo vices plus frequentemente que con leucemia lymphatic.

Isto es le prime serie de casos satis numerose pro permitter un analyse statistic del datos, con diagnoses invariabilmente provate per le constatactiones necroptic. Le conclusion es que tuberculose occurre infrequentemente in association con leucemia e non plus frequentemente que on expectarea in reportos de necropsias in general.

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PARASTERNAL CHONDRODYNIA (TIETZE'S SYNDROME)*

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As more reports of a particular clinical state are recorded, it becomes necessary to review the available pertinent data and to make appropriate changes in concept. This is the situation with the clinical entity which has been called Tietze's syndrome.¹ This syndrome was described originally in the German literature and later reported throughout Europe. However, to date only nine cases have been recorded in the American literature, and it is our belief that this small number does not reflect the true incidence of this curious syndrome. Moreover, certain features of the illness appear consistently and justify the adoption of a descriptive label; this would serve the purposes of both accuracy and wider familiarity. The observed consistency has prompted us to adopt certain diagnostic criteria.

CASE REPORTS

Case 1. On December 13, 1956, a 38 year old white male complained of having had left anterior chest pain for the preceding week. He had noted a tender swelling, and the pain was made worse with inspiration. The blood pressure was 140/80 mm. of Hg; pulse, 80; temperature, 98.6° F. Examination of the heart and lungs revealed normal findings. There was a swollen, tender area overlying the second left costal cartilage, with no skin changes. X-ray of the chest was within normal limits. The patient had immediate and complete relief following procaine infiltration. After remaining free of symptoms for two weeks he experienced a mild recurrence for two days, but this subsided spontaneously.

Case 2. A 30 year old white female sought help on August 3, 1957, for chest pain and localized tenderness which had bothered her for about a month. The only significant physical finding was a walnut-sized swelling over the second left costal cartilage which was exquisitely tender. The patient was assured of the benign nature of her distress. She refused procaine infiltration and her pain subsided two weeks later. She did not return a month later, as advised, but reported by telephone that the swelling had disappeared.

Case 3. A 33 year old white female was first seen on December 9, 1957, complaining of left anterior chest pain of two weeks' duration. One week before the onset she had had a mild upper respiratory infection with nonproductive cough. She had noticed a tender swelling at the site of her distress. Physical examination was within normal limits except for point tenderness at the left third costal cartilage, with slight swelling and palpable induration 2 cm. in diameter. The overlying skin was normal. The x-ray of the chest and electrocardiogram were normal. Local procaine infiltration resulted in immediate and lasting relief.

Case 4. This patient, a 64 year old white female, on November 6, 1957, sought relief of left anterior chest pain of three weeks' duration. Blood pressure was 140/80

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mm. of Hg; pulse, 72. The heart and lung findings were normal. There was a tender 4 cm. nodule overlying the left sternoclavicular cartilage. X-ray of the chest was normal. Local injection with procaine relieved her pain.

DISCUSSION

The American literature covering this syndrome comprises only three papers reporting nine cases. In 1953 Motulsky and Rohn¹ reported the first three cases in this country; two of these patients had Hodgkin's disease. Four more cases were added by Wehrmacher in 1955,² and two by Bernreiter in 1956.³

This syndrome consists of pain, tenderness and swelling involving cartilage adjacent to the sternum. The second costal cartilage appears to be involved most frequently, being affected in 60% of all cases.¹* Next in frequency is the sternoclavicular cartilage, then the third and, in decreasing frequency, the other costal cartilages. In 15% of cases there have been two of these sites of involvement. Pain is of moderate to severe intensity but may be slight, as in Tietze's original case. It is usually limited to the involved area, but at times may show surprisingly wide radiation. The pain is accentuated by deep respiration and by any movements that place a stress on the involved area. At times pain may be worse with weather changes, and, peculiarly, the recumbent position appears to aggravate pain in these patients. The patient is usually, but not always, aware of the swelling and tenderness. Swelling may be visible, but often it is detected only by widening of the cartilage and induration on palpation. The overlying skin is uninvolved and appears to be normal. The course is variable; the illness may cease spontaneously in a few days, or it may be continuous or remittent during months or years. The prognosis is excellent.

The differential diagnosis runs the gamut of all conditions producing pain in the chest, and has been detailed in other reports.^{1,2} In most instances the immediate problem is ruling out acute painful cardiovascular and pulmonary conditions. Obviously, this is essential.

In some instances tissue sections have been available, but the histologic changes described probably represent only normal variations.¹ This was the situation in Tietze's original case, and it suggests some process other than inflammatory or neoplastic.

In view of the benign nature of this syndrome, treatment is symptomatic. Heat and salicylates are helpful. X-ray therapy was tried but was found to be of little or no benefit.² The local infiltration of procaine has been employed previously.³ We used this method in three cases and obtained prompt and complete relief, lasting well beyond the time usually expected from procaine anesthesia. While it is reasonable to anticipate at least temporary control of pain from procaine infiltration into and around a small tender mass, the prolonged comfort afforded in these cases may indicate an interruption of some "vicious cycle."

* These figures are based on reports in the European literature.

Judging from the paucity of reports in the American literature, one might consider parasternal chondrodynia a rare clinical condition. However, in view of the four instances that have appeared in a short period among our private patients, we feel that it is probably more common than the few reports indicate. Diagnosis should cause no difficulty if the condition is kept in mind, and more frequent recognition of the syndrome can be expected if a greater clinical awareness is stimulated. It is to this end that we suggest the name "parasternal chondrodynia," a term that is descriptive and is within the confines of available evidence.

After a careful consideration of our experience with this syndrome and a review of other published case reports, we have stipulated for our use the following criteria for diagnosis:

1. Parasternal involvement of cartilage, manifested by tenderness and palpable swelling. Usually there are also pain and visible swelling.
2. Normal overlying skin.
3. Absence of other causative disease or trauma.
4. Relief of pain and tenderness by local infiltration of procaine.

SUMMARY

Four cases of parasternal chondrodynia (Tietze's syndrome) are reported, bringing the number in the American literature to 13. The clinical characteristics have been reviewed and discussed; criteria for diagnosis are listed, and a descriptive label is suggested.

SUMMARIO IN INTERLINGUA

Solmente novem casos de chondrodynia parasternal (syndrome de Tietze) se trova previamente reportate in le litteratura american. Quattro casos additional es hic reportate, augmentante le total a 13. Iste syndrome es plus commun que le cifras citate indica. Illo es characterisate per un spontanee tumescencia sensible de cartilagine al margine del sterno. Le suprajacente pelle es normal. Le cartilagine le plus frequentemente interessate es le secunde, postea le junction sternoclavicular, e finalmente le altere cartilagini. Le morbo pote durar dies o menses. Illo recurre frequentemente. Le infiltration de procaina allevia le symptomas. Il es importante distinguere chondrodynia parasternal ab dolorose morbos cardiac e pulmonar. Le autores propone le hic usate designation descriptive in loco del ancian termino syndrome de Tietze. Illes crede que le characteristics del syndrome justifica le adoption del sequente criterios diagnostic: (1) Sensibilitate e tumescencia de cartilagine al margine del sterno; (2) normalitate del pelle suprajacente; (3) absentia de altere morbos o trauma; e (4) alleviamento per le infiltration local de procaina.

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SEVERE TOXIC REACTIONS ASSOCIATED WITH SULFAMETHOXYPYRIDAZINE (KYNEX)*

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THE ever-increasing problem of bacterial resistance to antibiotics has caused a "shift of the pendulum" back to the usage of sulfonamides in recent years. This fact has again brought into the spotlight the clinical toxicity of these chemotherapeutic agents. With the development of newer and more soluble compounds, renal toxicity has virtually ceased to exist, and there has been a marked decline of other types of reactions to these drugs. In his evaluation of the newer sulfonamides, Yow¹ has listed their injurious effects as follows: fever, 1.5%; dermatitis, 1.5%; gastrointestinal toxicity, 1.3%; blood dyscrasias, 0.18%; hepatitis, 0.1%; renal toxicity, anaphylaxis, neurotoxicity, and superimposed infection, rare. Some of the factors that have been mentioned as influencing the incidence of these toxic reactions are: (1) duration and dosage of the drug; (2) structural formula of the compound; (3) solubility; (4) age and nutritional status of the patient; (5) re-administration of the drug; and (6) preexisting kidney disease or allergic diathesis.² These reactions, however rare, still do occur, and one must be prepared to encounter their potential dangers and to institute prompt and vigorous treatment.

The introduction of sulfamethoxypyridazine (Kynex),† one of the newest of these compounds, has made available a drug which combines rapid absorption from the gastrointestinal tract, high and prolonged plasma concentrations, and slow urinary excretion rate, thereby insuring rapid, adequate and sustained antibacterial levels with low doses given at infrequent intervals. It has been shown to produce only slight toxicity in experimental animals,³ and extensive clinical trials have indicated that adverse reactions are not unlike those produced by other sulfonamides in common usage.⁴⁻⁷

The purpose of this article is to report several cases of unusual, severe toxic manifestations associated with the administration of this drug observed at our institution.

CASE REPORTS

Case 1. A 31 year old white female was admitted to our service on August 15, 1957, with the chief complaint of rash and fever for two days. She was known to have chronic cervicitis and to have had a recent urinary tract infection; she had also

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had a cystorectocele for the last year. Shortly before admission she had been given sulfamethoxypyridazine in a dosage of 2 gm. the first day, followed by 1 gm. daily thereafter. Within 24 hours after taking the first dose she had had a warm feeling in her face and had become flushed. This continued until the morning of admission, when she awoke with a rash over her back that was pruritic. She immediately stopped taking the medication; however, the rash spread within a few hours to involve her entire body, and she became very anorectic. She was taking no other medications, and had no history of any allergies or rashes, and no knowledge of ever having taken sulfonamides.

Upon admission the blood pressure was 100/70 mm. of Hg; pulse, 110 per minute; respiration, 20 per minute; temperature, 104.2° F. orally. The skin was hot and dry, and presented a generalized erythematous papular rash which was discrete in some areas and confluent in others. Hemorrhagic areas were present in the center of many of the lesions. The patient's face was diffusely erythematous, and a bulbar and palpebral conjunctivitis with mucopurulent exudate and definite edema of the lids was present. The oral mucous membranes were diffusely red, and the tongue was ulcerated in some areas and contained a few vesicles in other areas.

Laboratory Data: Urinalysis showed an occasional white cell per high power field, and a blood count showed a mild leukopenia (4,400 cells per cubic millimeter), with a normal differential. Hematocrit, 41%; hemoglobin, 13.5 gm. per 100 ml. Blood urea nitrogen, carbon dioxide combining power, serum chlorides and fasting blood sugar were within normal limits. Serologic test for syphilis and blood and urine cultures were negative. An electrocardiogram was normal, and no L.E. cells were found. Precipitin tests for sulfamethoxypyridazine antibodies were inconclusive on two occasions.

Hospital Course: The fever responded dramatically to 300 mg. of intravenous hydrocortisone, 300 mg. intramuscularly, and 0.3 ml. aqueous epinephrine solution, 1:1,000 subcutaneously within the first 24 hours. Urinary output was always adequate, and the itching disappeared within a day.

After two days of cortisone therapy the patient developed a brief psychotic episode, with visual and auditory hallucinations, paranoid ideas and disorientation. A total 500 mg. of hydrocortisone had been given when the symptoms were first noted. The dosage was promptly reduced to 25 mg. twice a day, and the symptoms disappeared within four days.

After 10 days the acute skin lesions were gone, only a mottled faded rash remaining over the upper and lower extremities at the time of the patient's discharge from the hospital 15 days later. The white cell count had risen to 7,000, with 62% polymorphonuclear leukocytes, 36% lymphocytes and 4% eosinophils.

Case 2. A 54 year old Negro female was admitted to our service in March, 1958, after having been discharged three weeks previously with a diagnosis of bronchopneumonia and a urinary tract infection for which she was treated with procaine penicillin (600,000 units intramuscularly for five days) and sulfamethoxypyridazine (0.5 gm. twice daily). She was to continue the sulfa drug, and did so for 22 days, until two days prior to admission, when she experienced weakness and dizziness upon arising from bed and fell to the floor several times that day while attempting to get up. She also experienced a constant "bell-like noise" in her head, and felt as though she "was on fire."

That same morning the patient had developed a rash over her face, arms and trunk which quickly spread over her entire body. This rash was very pruritic, the itching becoming so intense that she had had her two grandchildren scratching her. She could not sleep, and refused to eat because of soreness of the mouth and inability to swallow.

The following day all of the symptoms increased, and the patient developed visual

disturbances described as transient episodes of blindness associated with chills, fever and drenching night sweats. She denied contact with any other drugs, had had no previous rashes, and there was no history of asthma, hay fever or any other allergies. There was a past history of syphilis, treated with bismuth in 1944, and chronic cervicitis of long standing.

On admission she presented as an acutely ill patient, unable to fix her attention on anything. Temperature, 104° F.; pulse, 134 per minute and thready; respiratory rate, 32 per minute and shallow. Blood pressure was reported at 140/70 mm. of Hg. An erythematous papular rash was present over the entire body, purplish and confluent in some areas. The buccal mucosa was erythematous, and contained many raised red papules and some vesicles, all coated with a thick, whitish pseudomembrane. A mucopurulent conjunctivitis was present, and the lips and nares were crusted and cracked. A soft protodiastolic basal murmur of aortic insufficiency was present.

Laboratory Data: Electrocardiogram showed left ventricular hypertrophy. Blood sugar was slightly elevated, and a diabetic type of glucose tolerance curve was present. Serologic test for syphilis was negative; six blood cultures were negative. Hematocrit, 40%; white cell counts, 6,000 and 11,000 cells per cubic millimeter, with 60% polymorphonuclear leukocytes, 36% lymphocytes and 4% bands on the first count and 42% polymorphonuclear leukocytes, 2% eosinophils, 1% basophils, and 55% lymphocytes on the second count; platelet count was normal. Initial urinalysis revealed 1 plus albuminuria, specific gravity was 1.015, and there was an occasional white cell per high power field. At the time of the patient's discharge 23 days later no albumin was present, and no white cells were seen in the urinary sediment. An L.E. cell preparation, and agglutination tests for typhoid H and O, *Brucella* and *Proteus* OX 19, were negative. One precipitin test for sulfamethoxypyridazine antibodies was negative.

Treatment consisted of epinephrine and aspirin only, in addition to "forcing of fluids." Within two and one-half days the patient's temperature had returned to normal values; it remained at 99.0° to 99.6° F. for another seven days, and was completely normal thereafter. After six days the skin lesions resolved into a fine macular rash, and after nine days the patient exfoliated. The skin was completely clear in three weeks.

Case 3. A 46 year old Negro female was admitted to the Medical Service of Charity Hospital on September 12, 1958, with the chief complaint of "sore mouth and running eyes." Since 1946 she had been suffering from intermittent attacks of bronchial asthma, and had received desensitizing injections at the Allergy Clinic over a period of two years. The asthma had continued, however, and in March, 1958, she presented suggestive roentgenologic evidence of bronchiectasis, although no bronchographic studies were ever obtained to substantiate this diagnosis.

The patient continued to be followed by the Chest Clinic, and remained asymptomatic except for a chronic, persistent cough productive of copious amounts of white sputum, and moderate wheezes and rhonchi throughout the chest. In January, 1955, she received a course of sulfisoxazole, without untoward effects.

The patient was admitted to this hospital in March, 1955, with an acute exacerbation of her cough. The sputum contained flecks of blood, and the patient developed fever. A diagnosis of bronchopneumonia was made, and she was treated with penicillin and sulfisoxazole, with success. The wheezing throughout both lung fields persisted, however. She was seen by a surgical consultant, who thought her bronchiectatic disease was too extensive to permit surgery.

In March, 1958, the patient's husband was found to have active tuberculosis. A thorough investigation of her sputum and gastric washings at that time showed no evidence of acid-fast infection. Her sputum continued to be produced in large quantities and contained occasional blood streaks. She was now followed in the

Medical Clinics. Postural drainage and antihistamines were of no avail, and she was put on sulfamethoxypyridazine, 1.0 gm. daily, on August 18, 1958. She took the drug until seven days prior to her final hospitalization (17 days).

Two days prior to admission the patient's eyes became red and were covered with a white exudate that prevented her from opening them. At this time she also developed painful weeping around the mouth and lips, with some difficulty in swallowing. An erythematous macular rash appeared over the anterior chest. The day before admission was marked by the onset of high fever and severe headaches. The rash became worse, and she was admitted on September 12, 1958.

There was no history of arthralgia, hematuria, melena or purpura. There were no cardiorespiratory complaints other than those listed above. The family, past and social histories were noncontributory. There was no history of drug intake except as above.

Physical examination revealed a moderately ill Negro female in some distress. Temperature, 104° F.; pulse, 110 per minute; respiratory rate, 20 per minute; blood pressure, 140/70 mm. of Hg. A severe conjunctivitis and purulent-like bilateral vesicular lesions over the mucosa of the lips, gums, mouth and soft palate were seen. Some of them appeared to be covered with white plaques. The chest was full of rhonchi, coarse râles and expiratory wheezes, but there was no evidence of consolidation, and the breath sounds were normally transmitted throughout. Examination of the heart revealed a tachycardia without murmurs or rubs. The liver and spleen were not felt, and no other masses were palpable in the abdomen. The skin showed an extensive maculopapular erythematous rash, with some areas of vesicular lesions over the anterior chest and back. Cervical and submandibular adenopathy was noted. Neurologic examination was grossly negative.

Laboratory Data: Hematocrit, 48%; hemoglobin, 14 gm. per 100 ml.; white blood cells, 8,050 per cubic millimeter, with 64% polymorphonuclear leukocytes, 3% bands, 2% eosinophils, 2% monocytes, 28% lymphocytes and 1% basophils. Urinalysis showed a pH of 5.5; specific gravity, 1.022, with 3 plus albumin, no sugar, and 50 to 60 white cells per high power field. There were numerous white cell clumps and granular casts. Sickle cell preparation, skin tests that included PPD No. 1 and fungal preparations were negative. Serologic test for syphilis, and febrile and heterophil agglutinations, were negative. Blood and urine cultures were negative. Viral cultures showed no growth. Blood urea nitrogen was 21.4 mg. per 100 ml.; carbon dioxide combining power was 25.7 mEq. per liter, and the fasting blood sugar was found to be 153 mg. per 100 ml. Precipitins to sulfamethoxypyridazine could not be demonstrated on one occasion. An initial diagnosis of Stevens-Johnson syndrome secondary to drug sensitivity was made.

Hospital Course: Penicillin (600,000 units twice daily), chloramphenicol (2 gm. per day), diphenhydramine (Benadryl) (50 mg. four times a day), and cortisone (75 mg. four times a day), were given. On the next day there was some objective improvement of the lesions. A dermatology consultant agreed with the diagnosis of Stevens-Johnson syndrome secondary to drug sensitivity, and the cortisone was increased to 600 mg. daily. ACTH injections of 25 units daily were also begun.

On the third day the patient was afebrile and much improved, but the following day the rash extended over the palms of the hands and soles of the feet. The mouth became so inflamed and swollen that she could not talk. Parenteral fluids and hydrocortisone, 600 mg. daily, were instituted. On September 18 the patient's condition deteriorated rapidly. Blood was discovered in the stool, and a chest film revealed increased densities in both lung bases, without definite diagnostic changes. An electrocardiogram was normal. The following day, vesicular and papular lesions were noted in the vaginal mucosa. Her condition gradually worsened, and on September 22 the temperature rose to 102.6° F. rectally, the pulse was now 120 per minute, res-

piratory rate was 36 per minute, and the blood pressure was 90/60 mm. of Hg. There were decreased breath sounds in the left lung base. Erythromycin (1 gm. daily) and nasal oxygen were added to the therapeutic régime, but the temperature rose steadily to 105° F. on the following day; the blood pressure became unobtainable, and the patient died on the eleventh hospital day. Permission for autopsy was obtained. On the day of death the hematocrit was 40%; there were 64,000 white blood cells per cubic millimeter, and a blood culture grew out an *Aerobacter* organism. Final clinical diagnosis was terminal septicemia complicating Stevens-Johnson syndrome secondary to drug sensitivity.

Autopsy findings were limited to typical gross and microscopic skin lesions of erythema multiforme as described above, plus extensive bronchiectasis, with evidence of acute and chronic inflammation of the lung parenchyma. The larger bronchi contained copious amounts of mucopurulent exudate. The liver revealed a minimal amount of fatty infiltration microscopically, and the kidneys exhibited microscopic evidence of a mild exudative glomerulitis. Postmortem blood culture showed *Aerobacter* and gram-positive cocci which were not identified further. Careful examination failed to reveal any evidence of visceral lesions which could be attributed to hypersensitivity phenomena.

DISCUSSION

Each of our patients received sulfamethoxypyridazine within seven days of the onset of the symptoms. Case 2 received five days' therapy with procaine penicillin, the last injection given 18 days prior to the onset of the illness, but this patient was taking the sulfonamide up to the time that the symptoms appeared, and improvement followed its discontinuance.

Skin rashes related to sulfonamides have been noted to occur any time between one and 37 days following the initiation of therapy.^{8, 9} They are seen most commonly between the seventh and the tenth days, according to Hageman and Blake.¹⁰ Two of our patients had 14- and 22-day courses of the drug; one (case 1) developed symptoms on the first day of therapy. The acute phase of the rashes disappeared within three weeks in case 2, and within 10 days in case 1.

Precipitin tests in all of our patients were negative for circulating antibodies to sulfamethoxypyridazine; however, it should be noted that in the past, attempts to demonstrate precipitins in the blood, as well as patch and intradermal tests, have been inconclusive.^{10, 11}

Case 1 developed a brief psychotic episode that included paranoid tendencies, visual and auditory hallucinations, and disorientation. These manifestations appeared two days after steroid treatment was instituted. It is uncertain whether this was the result of vigorous steroid therapy or on a basis of an allergic vasculitis related to the sulfa drug. Psychotic episodes of this nature have been described in association with earlier sulfonamides,⁸ but those related to steroids also occur frequently about this same time.^{12, 13}

Bullous skin lesions accompanied by ocular and oral mucosal manifestations have been described in association with the use of the earlier sulfonamides.¹⁴⁻¹⁷ We were able to find several fatalities resulting from severe episodes of this nature that followed the administration of sulfonamides.¹⁸⁻²⁰

Our cases resemble closely those associated with the earlier drugs. This combination of signs and symptoms fulfills the criteria for the diagnosis of Stevens-Johnson syndrome.²¹ To our knowledge, only one case of this kind has been reported in association with sulfamethoxypyridazine,²² and no deaths have occurred. Reactions to this drug have been limited to headaches, rashes, fever, abdominal pain, dizziness, nausea^{5, 6, 23, 24, 25} and, recently, to focal hepatitis,⁸ thrombocytopenia and leukopenia.²³

In addition to our case reports, other, less serious manifestations of toxicity to this drug have been observed on our service. These have included one severe asthmatic attack, consisting of respiratory distress, cyanosis, giant urticaria and enlarged submaxillary glands which required the use of steroids; and some instances of prolonged urticaria, nausea, vomiting and mental depression.

It should be mentioned that case 3 developed extensive terminal bronchopneumonia. This development has frequently been recognized in fatal cases of Stevens-Johnson syndrome.^{27, 28} The etiology of the pneumonia is uncertain, and there is no definite correlation between its appearance and the severity of the lesions.²⁰ Attempts to ascribe a viral etiology to this process have been inconclusive. Finland et al.²⁹ found elevated psittacosis complement fixations and cold agglutinins in some instances of this complication. It is possible, though, that in our case the onset of pneumonia was related to the general debilitated condition of the patient, and to the previous presence of bronchiectasis.

Many microscopic findings have been described in association with the administration of sulfonamides. These include such lesions as focal areas of hemorrhage and necrosis, and various types of granulomatous lesions, plus vascular and perivascular focal inflammation.^{30, 31} These changes were not demonstrable in our fatal case.

SUMMARY

Three cases of severe reactions to sulfamethoxypyridazine, one fatal, have been reported. The clinical picture met the criteria for the diagnosis of Stevens-Johnson syndrome. To date, no deaths have been reported in association with this drug. Sulfamethoxypyridazine is undoubtedly a valuable therapeutic contribution, but it is not exempt from serious and dangerous side-effects, as one may be led to believe from the results of previous investigations. It may be associated with untoward reactions involving a multiplicity of systems, among which are the skin, the gastrointestinal tract, and the respiratory, the hematopoietic, and possibly the central nervous systems.

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SUMMARIO IN INTERLINGUA

A causa del crescente problema de resistentia bacterial contra le antibioticos, le sulfonamidos es de novo usate plus extensemte in nostre dies. Assi le problema de lor toxicitate clinic ha devenite acute.

Sulfamethoxypyridazina, un relativemente nove sulfonamido, es popular in usos medical a causa de su rapide absorption ab le vias gastrointestinal, su alte concentration in le plasma, e su lente excretion urinari. Iste characteristicas del droga assecura adequate nivelloes de illo in le sanguine in despecto de basse dosages que pote esser administrata a infrequent periods.

Tres casos de grados sever de toxicitate associate con le administration de iste droga—incluse un morte—esseva observate in le salas medical del Hospital de Caritate. Le combination del signos e symptomas in iste casos satisfaceva le criterios diagnostic del syndrome de Stevens-Johnson. Altere manifestationes de toxicitate—de grados minus alarmante de severitate—esseva observe e es describite brevemente. Isto include plure casos de prolongate urticaria, nausea, vomito, e depression mental, e, in plus, un attacco asthmatic con sever angustia respiratori, urticaria gigante, cyanosis, e allargamento del glandulas maxillari que requireva le uso de steroides.

Teste de precipitina pro circulante anticorpore anti sulfamethoxypyridazina esseva negative in le tres casos sever. Previe essayos de demonstrar precipitinias in le sanguine e etiam tests de timbro e tests intradermal ha remanite inconclusive.

Le reporto necrotic in le caso mortal non revelava ulle constataciones microscopic previamente reportate como associate con le administration de sulfonamidos, como per exemplo varie typos de lesiones granulomatose, inflammation focal vascular e perivasicular, o areas focal de hemorrhagia e de necrosis.

Sulfamethoxypyridazina, ben que de valor therapeutic, non es libere de periculose effectos lateral, per contrasto con le impression que on pote derivar ab previe reportos. Iste reactiones adverse pote afficer multe differente systemas organic, incluse le vias gastrointestinal e le systemas respiratori, hematopoietic, e possibilmente nervose central.

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LUNG VOLUME IN SMOKERS AND NONSMOKERS * †

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TOBACCO smoking has long been suspected as an etiologic factor in respiratory symptoms and chronic bronchopulmonary disease, largely on the basis of clinical impression. Recent evidence tends to confirm this impression. Auerbach and associates reported greater prevalence of pathologic changes in the bronchial mucosa of smokers than in nonsmokers.¹ Eich, Gilbert and Auchincloss found increased airway resistance as an acute effect of cigarette smoking in a few patients with pulmonary emphysema. They observed no change in pulmonary mechanics after smoking in normal subjects.² In Higgins' field study of a random population sample in England there was evidence of reduced ventilatory capacity (peak flow rates) in smokers.³ A number of epidemiologic reports have suggested that there is an increased prevalence of cough, chronic bronchitis, obstructive emphysema and lung cancer in smokers vis-à-vis nonsmokers.⁴⁻¹¹ Little has summarized valid criticism of the methodology and conclusions of certain of the epidemiologic studies on smoking and lung cancer, and has questioned the conclusions drawn from pathologic studies of bronchial mucosa.¹² There is no convincing cause-and-effect link in this picture to date, but the existence of statistically significant associations between smoking habit and lung disease is more evident with the passage of time.^{13, 14} Berkson has pointed out that statistically significant associations between the smoking habit and *many* chronic diseases may be found, and that this may indicate a more fundamental relationship between smoking, aging and illness than simple cause-and-effect for any single malady.¹⁵

Measurement of anatomic lung compartments in older individuals might be expected to provide some information concerning ultimate lifetime effects of smoking on bronchopulmonary function. Lung volume measurements were made in a group of middle aged males on whom good information about smoking habit was available, and from whom the effects of age and body size on these variables could be eliminated. The small but interesting differences in lung volumes between smokers and nonsmokers make up the substance of this report. Studies more pertinent to the mechanics of respiration in

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smokers and abstainers are in progress in this and other groups of "normal" males.

METHOD

Data are available for 221 business and professional men of the Twin Cities. These men have participated in a 10-year longitudinal study of cardiovascular aging. The age range at the time of lung volume measurement was 47 to 57 years—mean age, approximately 52 years. The subjects were selected from 916 acceptances to 1,000 invitations, issued in co-operation with several Twin City business, industrial and professional organizations, and were randomly chosen to fill categories of different relative body weights. We believe it unlikely that any bias occurred from the manner of selection, per se, which would weight smoking categories with subjects having respiratory illness. All subjects were actively employed and were free of manifest heart disease or hypertension of 150/100 mm. of Hg or above, and none had gross parenchymal lung involvement on chest x-ray.

Smoking questionnaires comparable to those of the American Cancer Society¹⁰ were administered by the Laboratory staff, and classification of cigarette smoking habits was made according to the following criteria:

"Never": Either never smoked, or had had only slight and remote cigarette smoking experience.

"Occasional": Not daily.

"Light": One to 10 cigarettes a day, regularly.

"Moderate": 10 through 20 cigarettes a day.

"Heavy": Over 20 cigarettes a day.

"Stopped": Includes those who had successfully stopped *all* types of smoking for at least a year, on the basis of two annual interviews.

The dominant smoking pattern was determined largely on the basis of the smoking experience during the preceding five years, with the intensity at the time of the study as the principal reference point. This study is chiefly concerned with cigarette smoking habit. However, those placed in the "Never" cigarette category who had more than a "Light" classification for cigar or pipe (over two cigars or five pipefuls daily) were analyzed separately.

Subjects reported to the Laboratory at 8 a.m. in a fasting state, and smoking was proscribed during the morning activities. Following a 30-minute rest, and determination of basal oxygen consumption, a sitting vital capacity was recorded. The larger value of two determinations was utilized. The instrument was a standard Sanborn spirometer, and readings were made with an accuracy of ± 60 c.c. The subjects had had previous experience with vital capacity measurements in this laboratory.

Residual air volume determination was begun after forced expiration while the subject was totally submerged in water in a sling seat. This tech-

nic was used to arrive at a more accurate measure of body density, and has been previously reported.¹⁶ The differences between residual volume measured after forced expiration under water and in room air are insignificant and will be described. The open circuit nitrogen dilution method of Cournand and associates was employed, with the slight modifications necessitated by the underwater technic.¹⁷ Two or more preliminary weighings were made underwater at the end of a forced, maximal expiration. If two or three weighings checked within ± 100 gm. it was concluded the subject was "trained" in the method, and minimal values of residual volume could be approximated. On the final submersion, when weight reached the previously established level, the communicating valve was turned for pure O₂ breathing with exhalation into the Tissot gasometer. The subject was immediately raised above water and seven-minute oxygen breathing completed. No alveolar samples were taken. A mean value of duplicate gas samples from the Tissot was used for computation, and residual volume was calculated after the method of Cournand, Baldwin, Darling and Richards.¹⁷ Nitrogen excreted through the lungs during the period of oxygen breathing was estimated on the basis of data from Cournand, Yarmush and Riley.¹⁸ A nitrogen concentration of 79.8% was the value assumed for the denominator of the equation of Cournand and associates. This is based on assumptions following early findings and suggestions of Cournand and associates of 81.0% N₂ for the initial alveolar sample, and their finding of approximately 1.2% N₂ for the mean end-alveolar sample in "normal" subjects.¹⁸ The validity of these assumptions and their effect on the resultant of the equation will be considered in the discussion. Volumes were corrected for temperature and vapor pressure. The subjects were experienced in underwater weighing from previous examinations in the laboratory. Relative body weight was calculated from standards given in the 1912 Medico-Actuarial tables.

RESULTS

Cigarette smoking categories alone are considered in presentation of the data. Table 1 contains means and standard deviations for age, height and relative body weight in each smoking category. The similar mean ages (together with the narrow range of age, limited to one decade) and similar body size as expressed by height and relative body weight eliminate age and body size as variables in the lung volume comparisons between smoking groups. The differences in means of these variables nowhere approach statistical significance.

Table 2 presents means and standard deviations for vital capacity, residual volume (RV), total lung capacity (TLC), and RV/TLC as per cent, for each smoking category.

Table 3 presents differences in means for lung compartments and their statistical significance, between "Never" versus "Moderate," "Heavy,"

TABLE 1
Age, Height and Relative Body Weight of Middle Aged Male Smokers and Nonsmokers
(N = 221)

| Smoking Category | Never | Occasional and Light | Moderate | Heavy | All Smokers Combined | Stopped |
|--------------------------|-------|----------------------|----------|-------|----------------------|---------|
| N | 65 | 38 | 54 | 33 | 125 | 31 |
| Age (years) | M | 52.0 | 51.5 | 51.5 | 51.3 | 52.5 |
| | SD | 3.0 | 3.0 | 3.4 | 3.1 | 3.6 |
| Height (cm.) | M | 176.0 | 173.8 | 175.5 | 176.3 | 175.2 |
| | SD | 6.3 | 6.1 | 6.6 | 6.0 | 6.4 |
| Relative body weight (%) | M | 100.6 | 102.4 | 98.8 | 100.2 | 98.8 |
| | SD | 14.5 | 14.3 | 13.3 | 15.1 | 14.1 |

"Combined" (O + L + M + H) and "stopped" categories of cigarette smokers.

Vital capacity was less in each category of smokers than in nonsmokers ("Never"), and was significantly smaller in all smokers combined (211 c.c.) ($P < .05$). Residual volume was larger in all categories of smokers, but the difference was statistically significant only between the "Never" and the "Moderate" groups (260 c.c.; $P < .01$). Differences in total lung capacity between groups were small, inconsistent, and in no instance statistically significant. The ratio of residual volume to total lung capacity was higher in each smoking category at significance levels slightly above or below 1%. Twelve individuals in the "Never Smoked" category had pipe or cigar smoking habits judged to be "Moderate" (over two cigars or five pipefuls of tobacco daily). Elimination of these individuals made only minute changes in the means for the "Never" group, and did not affect the significance of differences between groups.

Thirty-one individuals who had moderate or heavy lifetime smoking

TABLE 2
Lung Volumes in Middle Aged Male Smokers and Nonsmokers
(N = 221)

| Smoking Category | Never | Occasional and Light | Moderate | Heavy | All Smokers Combined | Stopped |
|----------------------------|-------|----------------------|----------|-------|----------------------|---------|
| N | 65 | 38 | 54 | 33 | 125 | 31 |
| Vital capacity (c.c.) | M | 4320 | 4033 | 4153 | 4125 | 4109 |
| | SD | 678 | 734 | 656 | 513 | 644 |
| | | | | | | 4349 |
| | | | | | | 575 |
| Residual volume (c.c.) | M | 1890 | 1917 | 2150 | 2003 | 2040 |
| | SD | 376 | 618 | 699 | 370 | 608 |
| | | | | | | 1920 |
| | | | | | | 338 |
| Total lung capacity (c.c.) | M | 6228 | 5990 | 6309 | 6149 | 6170 |
| | SD | 897 | 902 | 1013 | 682 | 905 |
| | | | | | | 6262 |
| | | | | | | 764 |
| RV/TLC (%) | M | 30.6 | 32.5 | 33.8 | 32.9 | 33.2 |
| | SD | 4.1 | 8.5 | 6.9 | 4.5 | 6.9 |
| | | | | | | 30.5 |
| | | | | | | 4.1 |

TABLE 3
Differences in Means of Lung Volumes and Their Significance in Smokers vs. Nonsmokers
(N = 221)
(N = Never; M = Moderate; H = Heavy; C = Occasional + Light + Moderate
+ Heavy; S = Stopped)

| Smoking Category | M—N | H—N | C—N | S—N | C—S | |
|----------------------------|--------|--------------|--------------|---------------|-----------|--------------|
| N1 + N2 | 119 | 98 | 190 | 96 | 156 | |
| Vital capacity (c.c.) | M t | -167 1.36 | -195 1.45 | -211 2.10* | 29 — | -240 1.89 |
| Residual volume (c.c.) | M t | 260 2.69† | 113 1.45 | 150 1.88 | 30 — | 120 — |
| Total lung capacity (c.c.) | M t | 82 — | -79 — | -38 — | 34 — | -92 — |
| RV/TLC (%) | M t | 3.2 3.11† | 2.2 2.46* | 2.5 2.72† | -0.1 — | 2.6 2.01* |

* Pt = <.05

† Pt = <.01

habits and had successfully stopped all forms of smoking one or more years prior to the date of lung volume measurement had values very close to those of the nonsmokers. No significant differences were found between the means of "Stopped" vs. "Never" categories. Vital capacity was greater (at a level approaching statistical significance) in the "Stopped" group than in the combined smokers, currently smoking, and RV/TLC% significantly less ($P < .05$).

The over-all mean values obtained for vital capacity and residual volume in these subjects (mean age, 52 years) compare well, in general, with values found by others in "elderly normal" individuals.^{20, 21} The slightly younger

TABLE 4
Lung Volumes in Middle Aged Male Smokers and Nonsmokers
(Sample screened of clinical respiratory manifestations)
(N = 188)

| Smoking Category | Never | Occasional and Light | Moderate | Heavy | All Smokers Combined | Stopped |
|----------------------------|---------|----------------------|-------------|-------------|----------------------|-------------|
| N | 55 | 33 | 43 | 27 | 103 | 30 |
| Vital capacity (c.c.) | M SD | 4362 694 | 4053 683 | 4241 621 | 4125 561 | 4150 626 |
| Residual volume (c.c.) | M SD | 1872 388 | 1848 502 | 2133 498 | 2015 374 | 2009 484 |
| Total lung capacity (c.c.) | M SD | 6247 940 | 5943 959 | 6373 892 | 6166 732 | 6181 887 |
| RV/TLC (%) | M SD | 30.1 4.0 | 31.7 5.7 | 33.3 5.5 | 33.1 4.8 | 32.7 5.4 |

average age, greater height and excellent physical status of this group probably explain such differences as do occur.

We were interested to determine the influence of a very careful screening for clinical respiratory manifestations in the present sample of 221 active males. This was done systematically, according to the criteria indicated below. Values were eliminated for subjects in whom any of the following manifestations occurred:

1. History of any clinical asthma or pulmonary tuberculosis.
2. History of chronic productive cough.
3. History of chronic cough or dyspnea with findings of expiratory lag, wheezes or râles.
4. History of chronic cough or dyspnea with x-ray findings compatible with bronchitis, fibrosis or emphysema.
5. Findings of prominent wheezes or expiratory lag alone.
6. Finding of prominent chest deformity.

TABLE 5

Differences in Means of Lung Volumes and Their Significance in Smokers vs. Nonsmokers
(Sample screened of clinical respiratory manifestations)
(N = 188)

(N = Never; M = Moderate; H = Heavy; C = Occasional + Light + Moderate
+ Heavy; S = Stopped)

| Smoking Category | M-N | H-N | C-N | S-N | C-S |
|----------------------------|--------|--------------|--------------|---------------|-------------|
| N1 + N2 | 98 | 82 | 158 | 85 | 133 |
| Vital capacity (c.c.) | M t | -120 — | -237 1.51 | -211 1.95* | -5 — |
| Residual volume (c.c.) | M t | 260 2.98† | 143 1.62 | 137 1.86 | 58 — |
| Total lung capacity (c.c.) | M t | 126 — | -80 — | -66 — | 34 — |
| RV/TLC (%) | M t | 3.1 3.25† | 3.0 2.93† | 2.6 3.75† | .5 — |
| | | | | | 2.1 1.80 |

* Pt = <.05

† Pt = <.01

Thirty-three subjects were excluded by these rather stringent criteria. Eleven were "Never" or "Stopped" smokers, and 22 were smokers. No significant difference in mean age or body size between smoking categories appeared on elimination of values for these subjects.

In table 4 the same general relationships between smokers and nonsmokers as in table 2 were found in comparing the means for vital capacity, residual volume, total lung capacity and RV/TLC. In table 5 the statistical significance of the differences in means between smokers and nonsmokers is of the same order of magnitude as in the total sample.

COMMENT

There are several older studies of lung volumes in normal individuals examined with reference to smoking habit. Earp in 1925²² and Turley and Harrison in 1932²³ found no differences in vital capacity between smokers and nonsmokers. However, their subjects were young students with short smoking histories. In 58 healthy male subjects of considerable age range, Whitfield, Arnott and Waterhouse found significant correlations between intensity of recent tobacco consumption and vital capacity (r of -0.228) and residual volume (r of $+0.400$).²⁴ When the effect of age had been removed by calculating coefficients of partial correlation, the r values decreased to -0.097 and $+0.318$; only the association of smoking with residual volume remained statistically significant.

The present study has the advantage of a narrow spread in age of the subjects and similar mean ages for the different smoking categories. Thus the comparisons are not complicated by the fact that tobacco consumption may increase with age, while at the same time significant age changes in the subdivisions of lung volume may occur.

The results of the present study suggest that, in smokers compared with nonsmokers, there is a slightly smaller vital capacity and a larger residual volume, little difference in total lung capacity, and an increased residual volume/total lung capacity ratio. The differences suggested by the analysis of Whitfield and associates²⁴ are confirmed by these results in a larger, more uniform group.

If the arbitrary, clinically employed value of 35% for RV/TLC is examined with reference to smoking habit, 31.2% of smokers fall above this level, compared to 13.8% of nonsmokers in the sample of 221 men. The difference, tested by Chi-square, is significant (Chi-square = 5.93, $P = .015$). In the screened sample of 188 subjects the RV/TLC ratio was greater than 35% in 28.2% of smokers and in 9.1% of nonsmokers. The difference is significant (Chi-square = 6.63, $P = .01$).

Additional information is to be desired concerning the other lung subcompartments, and the end-alveolar sample values. The difference between underwater measurements of residual volume and those made in air would also be of interest. The purpose of underwater measurement of residual volume was to arrive at a more accurate determination of body density of these subjects, and not specifically to appraise pulmonary function. Poor exhalation underwater, resulting in elevated values for residual volume, would not be likely to occur more frequently in smokers than in nonsmokers.

It would be of considerable interest to study pressure-volume relationships in underwater respiration at this submersion depth. This not having been done, it is speculative whether the external forces to the chest might (a) tend to reduce differences between smokers and nonsmokers by greater expiratory efficiency on submersion, or (b) exaggerate the differences by augmentation of airway resistance in smokers, who may indeed have some

degree of bronchiolar obstruction. It appears likely that neither occurs in "clinically normal" individuals. We have only indirect evidence from measures of residual volume in air and underwater that the over-all differences in ability to perform a complete expiration are not great. The difference in air-water mean residual volume of 26 middle aged men from this group was minus 17 c.c., quite insignificant. In nine students the difference in mean values of residual volume in air-water was 136 c.c., also not statistically significant.¹⁰

Finally, the error of measurement resulting from the assumptions made for initial and terminal alveolar nitrogen concentration is not precisely known. In "normals" with end-alveolar N₂ concentrations under 2.5%, the error is likely to be in the neighborhood of 1 to 2%.¹⁸ The end-alveolar N₂ concentration was less than 2.5% in 12 of 15 subjects over age 65 recently studied by Pierce and Ebert,²⁵ while the mean value for RV/TLC was 45.1%, much higher than in this group. The figure of 79.8% N₂ in the denominator of the Cournand equation is of course larger than it should be for individuals with an obstructive ventilatory defect. However, this would reduce the resultant values for residual volume in any emphysematous subjects included, and, in turn, minimize differences between smokers and nonsmokers, if such individuals predominate in smoker categories.

It is inappropriate to draw conclusions concerning cause and effect from associations found in cross-sectional analyses. However, the hypothesis that lifetime smoking plays a role in differences in size of lung compartments found in middle age is strengthened by these several considerations:

1. In *each* category of middle aged male smokers the vital capacity is smaller and the residual volume larger than in nonsmokers. The observed differences are not, however, uniformly proportional to intensity of smoking.
2. The differences found are in the direction to be expected if smoking is a cause of repetitive bronchial irritation and increased airway resistance.
3. Individuals who have stopped smoking have lung volume values similar to those of nonsmokers, though "reversibility" of these "changes" is of course hypothetic.
4. Significantly more smokers than nonsmokers have clinically elevated residual volume/total lung capacity ratios.
5. Changes in the same lung measurements, of similar magnitude and direction, have been found by others in a study on a quite different population.

SUMMARY

1. Anatomic lung compartments were measured in a group of 221 middle aged males (mean age, 52 years) and mean values compared for subgroups of cigarette smokers and nonsmokers.
2. Age and body size were eliminated as variables in the lung volume comparisons.
3. Vital capacity was smaller in each category of smokers. The dif-

ference from nonsmokers reached a statistically significant level for all smoking categories combined.

4. Residual lung volume was larger in all categories of smokers, but not consistently at significant levels statistically.

5. Total lung capacity was not significantly different between groups.

6. The ratio of residual volume to total lung capacity ($RV/TLC \times 100$) was significantly greater in smokers.

7. In a group which had successfully stopped all smoking (on the basis of two annual interviews), the lung compartment values were similar to those of a group who had never smoked, and the RV/TLC was significantly smaller than in the current smokers.

8. Stringent screening of this sample for abnormal respiratory manifestations left a residual 188 men in whom the same order of differences in lung volume prevailed between smokers and nonsmokers as in the total sample.

9. The prevalence of an "elevated" ($> 35\%$) residual volume/total lung capacity ratio was significantly greater in smokers.

10. Differences in vital capacity, residual volume and RV/TLC were in the direction to be expected if smoking is a factor in producing a functional increase of airway resistance.

11. Comparable differences in lung volume have been found by others in a population examined with reference to smoking habit.

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This study was carried out in the broader context of investigations on the role of mode of life in development of chronic disease under the direction of Professor Ancel Keys. Statistical assistance was provided by Mr. Norris Schulz.

SUMMARIO IN INTERLINGUA

Anatomic compartimentos pulmonar esseva mesurate in un gruppo de 221 masculos de etate medie, e le valores obtenite esseva comparate inter le sub-gruppos de fumatores e non-fumatores. Le etate medie del subjectos esseva 52 annos, con 10 annos como differentia inter le etate minimal e le etate maximal. Le dimensiones del corpore esseva simile in fumatores e non-fumatores. Le capacitate vital esseva plus micre in fumatores, le volumine residue esseva plus grande in illes, lor total capacitate pulmonar non differeva significativemente ab illo del non-fumatores, e le proportion inter volumine residue e total capacitate pulmonar esseva significativamente plus grande in fumatores que in non-fumatores. Le elimination, ab le gruppo initial, de omne le subjectos con manifestaciones respiratori anomal resultava in un gruppo residue de 188 homines pro qui le mesme ordine de differentias del volumine pulmonar esseva constatare inter fumatores e non-fumatores. Le prevalentia de un proportion inter volumine residue e total capacitate pulmonar de plus que 35 pro cento esseva significativamente plus alte inter le fumatores.

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DEPRESSION, SUICIDE AND SUICIDAL GESTURE IN MEDICAL PRACTICE *

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MENTAL depression affects the organism as a whole. In many ways it is a systemic illness and, like other generalized or systemic illnesses, may manifest itself in widely variable forms. The symptoms of depressed patients are by no means limited to complaints pertaining to mood, ambition, emotional despondency, etc. A depressed patient will often experience change in almost every aspect of his life. His entire world seems different; his future seems different; his body seems different; his bodily functions seem different. The depressed patient frequently presents to his physician any one of a number of somatic complaints as the primary focus of his concern. Indeed, the psychiatrist is rarely the first physician consulted, even when the patient is severely depressed.

Physicians in all medical specialties are called upon at times to diagnose and to treat patients who are depressed, and who threaten or attempt suicide. Without doubt, many of the acknowledged 16,200 suicides each year in this country¹ are the result of a diagnostic or therapeutic failure with patients suffering from serious depressive illness. (The reported total of 16,200 is very likely only a fraction of the total number: the social stigma of suicide, along with insurance considerations, may result in a great deal of covering up by the patient, his family and others.) The family physician is frequently the person to whom the depressed patient turns prior to making serious self-destructive attempts.

WHAT IS DEPRESSION?

Depression from the Viewpoint of the Depressed Patient: From the perspective of the depressed patient, there could be no more discouraging, dispiriting and terrifying disease. Patients with even the most serious of physical illnesses rarely experience the sense of hopelessness that is characteristic of many depressed patients. Early in the course of depressive illness, pessimism, a sense of "something wrong," apprehension and some degree of despondency are characteristic symptoms. Late in the course of depression of psychotic proportion, the patient may be in a state of profound agitation and collapse. He may be agitated to a point where sustained sleep is impossible; he may be hopelessly deluded, or deeply self-accusatory. Such patients view suicide as the only logical escape from their situation.

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Not all periods of despondency, downheartedness and discouragement represent a threat to life. Indeed, there are very few people who have not experienced periods of frank depression at some time in their lives. Periods of mourning associated with death, loss of a love object, or business or professional failure may serve as examples of appropriate response to the reality of the situation. Mild depression is also a frequent concomitant of the days following some kind of excess, either alcoholic or emotional, or in the "let-down" period following some interval of heightened effort. Many patients report the presence of subtle discouragement and downheartedness during the prodromal period of some viral infections. Ordinarily, however, these periods of depression are relatively short-lived, and separation from the precipitating cause leads to recovery. It may be important to state that periods of despondency which persist long after great stress cannot be understood as merely "reactive depressions." When the period of depression following some loss seems inordinately severe or prolonged, the physician does well to ask himself whether his patient is not suffering from a medically treatable emotional illness. Of course, physical illness in general may be very dispiriting, and some illnesses, such as carcinoma of the pancreas, may be heralded by pervasive despondency.

In some individuals there is a lifelong inclination to be depressed, and in these patients depression can thus be understood as a "way of life." These individuals are constantly discovering pessimistic fulfillment of their discouraging expectations. Their lives are characterized by few periods of uncomplicated joy; on the other hand, there is usually a limit to the intensity of their depression. Ordinarily, these chronically disgruntled individuals rarely prove to be suicidally inclined. Indeed, depression and pessimism constitute a defense which anticipates and thereby diminishes the impact of disappointment.

For the average person, however, depression represents a decided change in his over-all outlook on life. The patient is ordinarily quite impressed by the fact that a change has taken place within himself in the way he sees things. He may describe self-doubt, generalized fearfulness, morbid preoccupation, fear of meeting people, and difficulty in the performance of ordinarily simple tasks. Patients often describe a most distressing sleep disturbance, and the early morning hours frequently represent the lowest and most difficult time of their day. When asked to compare his life at the moment with his life at some time in weeks or months before, the truly depressed patient will often describe a change of black-and-white proportion.

The intensity and pervasiveness of the severely depressed patient's symptoms are frequently very difficult for the inexperienced person to comprehend. In the authors' experience, a failure to estimate the gravity of depression is the error most frequently made in the diagnosis of emotional illness.

The Physiopathology of Depression: In recent years there has been a great deal of interest in and study of the possible elaboration of neuro-

anatomic or neurochemical aspects of depression. Nevertheless, it is not yet possible to describe either anatomic or physiochemical defects which are inevitable (or frequent) concomitants of clinical depression.

An important recent contribution has been the development of the "sedation threshold," devised by Shagass and his associates in Montreal.^{2,3} These authors were able to demonstrate marked test differences between groups of "neurotic depressives" and groups of "psychotic depressives." Definite group differences were demonstrated in terms of the amount of sodium amytal per kilogram of body weight necessary to produce certain characteristic electroencephalographic changes. Results to date with the use of the sedation threshold suggest the possible role of an adrenergic component of the reticular system in the upper brainstem in the mediation of anxiety. These authors propose that there may be inhibitory neural components which are especially active in severe or psychotic depression. The neurophysiologic studies of French, Verzeano and Magoun had previously called attention to the segment of the upper brainstem adjacent to the diencephalic area as intimately involved in an "alerting system" influencing the level of consciousness.⁴ These research studies suggest that there may be "inhibitory" and "alerting" neural components in the brainstem which are subject to excess activity or suppression, and that such neural components may play an important role in mediating states of depression or elation.

In his recent book, Kraines⁵ concludes that most depressions are related to some disturbed physiologic function of the diencephalon, rhinencephalon, and associated reticular formation, and that the etiology of this disturbance lies in hereditary and/or hormonal pathology. He feels that there is strong clinical evidence suggesting physical factors as etiologic forces in these illnesses. These clinical observations include the occurrence of depressive illnesses in the absence of known predisposing or precipitating psychic factors, the response of depression to such physical therapy as electric shock, a marked influence of heredity, and the frequent onset of depression after childbirth, even in women with stable personality backgrounds.

Over the years the pharmacologic treatment of depression has been disappointing in both its therapeutic and its potential research aspects. The use of drugs producing cerebral stimulation, such as the amphetamines and methyl-phenidylacetate (Ritalin), occasionally provides mild relief of depression, but often there are accompanying tension, insomnia, diminished appetite, etc. These stimulating drugs often seem to have an effect comparable to that of "whipping and urging the tired horse." In recent years, several drugs have been developed which appear to demonstrate promising antidepressant action. One of these medications, Marsilid,* was used initially as a potentiator of streptomycin in the therapy of tuberculosis. The marked increase in sense of well-being in some tuberculous patients led to its experimental application in depression. There is evidence that Marsilid

* Iproniazid, Roche.

inhibits mono-amine oxidase, thereby slowing down the inactivation of tissue formed serotonin.⁶ Another drug, Deaner,* has been recently introduced in the pharmacotherapy of depression. This agent is felt to be a possible precursor of acetylcholine, and may act as a central nervous system stimulant, lowering the threshold for stimulation of the reticular formation and the diffuse thalamic projection systems.⁷ It is likely that within the next few years there will be increasing effort to unravel such neurophysiologic and neurochemical reactions as may accompany or produce clinical depression.

Psychopathology of Depression: Many of the symptoms of depressed patients seem quite paradoxical. Some patients seem determined to end their lives as if no longer moved by an instinct for survival. Some depressed individuals of great wealth and property think of themselves as bankrupt; patients whose life histories have been characterized by achievement, social consciousness and morality are deeply self-accusatory of the vilest of sins. There has been much speculation with regard to the content and meaning, i.e., "psychopathology," of depressive illness. Freud,⁸ following the work of Karl Abrahams,⁹ attempted to compare depression with its "normal" counterpart of melancholia in grief. He felt that depression represented an exaggerated and morbid form of grief. In later deliberation of Freud's work, the loss of a loved object remained the classic model of the depressive reaction. It should be noted that the loss of a loved object refers not only to the loss of some loved person by death or desertion, or to the loss of some loved possession, but also to the loss of a function, as, for example, certain youthful abilities which diminish with advancing age. Freud felt that in both mourning and depression there are unwillingness to surrender the loved object and an incapacity to reinvest the love and interest freed by this loss in other objects. This leads to withdrawal of interest in the world. In depression, this withdrawal is combined with self-accusations and strong guilt feelings toward the lost but not actually surrendered loved object. Freud explained this on the basis of strong mixed feelings toward the lost loved object (a combination of love, hate and guilt).

In recent years, psychodynamic attention has been focused upon the way an individual experiences himself and his world when in a depressive state. These experiential characteristics include a decrease in self-esteem, a more or less intense feeling of helplessness, and a more or less extensive inhibition of functions. The depressed person may be severely disappointed in himself because he finds he is faced with overwhelming powers against which he feels absolutely helpless. It makes no difference whether this is a reality situation or an imagined situation, i.e., whether outer or inner reality. The loss of a loved object, such as the death of a loved person, represents only a particular example of the way an individual may experience his own helplessness and incapacity in the world.

Are there psychodynamic factors which predispose an individual to a

* Dimethyl aminoethanol, Riker Laboratories.

depressive reaction? Are there particular kinds of personality structures especially vulnerable to the development of a depressive state? Is there evidence that depression is related to early traumatic experience, such as some deprivation of vital needs, causing the infant or child to experience undue helplessness, frustration, anger and depression? In reality, these questions remain essentially unanswered. One often hears the belief expressed that the older adult who becomes depressed is an individual who was too conscientious, too striving, too highly ordered, likely to have been somewhat on the obsessive side. These individuals are thought to have placed heavy emphasis upon "things," the accumulation of money and other material objects. With advancing age, achieving, doing, possessing, and emphasis upon the material become much more difficult. Competition is keener, and the incentives earlier present for such pursuit of material goals may be lost.

THE "CHIEF COMPLAINT" OF DEPRESSED PATIENTS

If the platitude which warns against treating symptoms rather than people has any application, it is to the patient who suffers from a depressive illness. More often than not the depressed individual presents himself to his physician with complaints referable to general physical health. Early in the course of a depressive illness a patient may experience a state of general alarm, characterized by hyperalertness, tension, apprehensiveness, and a pervasive feeling that something is wrong. The focus of concern is often tied to some physical complaint, i.e., concern about constipation, fear of cancer, fear of a brain tumor, pains in the chest or abdomen, or concern with regard to almost any body area or bodily function. The patient may be sleeping poorly, perhaps awakening early in the morning, and there may have been a sustained loss of appetite with accompanying weight loss. At times, such a patient is found to have a marked elevation of blood pressure which may diminish when his depression has improved. Sometimes he will express more frankly his psychologic concerns, such as worry about business, guilt over past sins, or apprehension about some impending event within the family. Of much importance, of course, is the physician's capacity to recognize the emotional state of the patient, to be attentive to the fundamental downheartedness, the underlying overconcern, the pervasive discouragement beneath the patient's description of his complaints.

Late in the course of a depressive illness the patient may seem to be profoundly inert rather than agitated. In this psychotic state he may manifest "psychomotor retardation," present a rather dazed and retarded appearance, and speak in a monotone.

It goes without saying that patients with gross depression have been treated fruitlessly for a wide variety of somatic conditions. Older patients in particular are likely to have been treated for such conditions as "spastic bowel," hemorrhoids, high blood pressure, insomnia and urinary difficulties, without recognition by the physician of the fundamental pathologic process.

AGE IN DEPRESSION

Early Childhood and Preadolescence: Depressive illness, suicide and suicidal gesturing do occur in childhood, if somewhat infrequently. Indeed, there is probably a very marked tendency on the part of parents and physicians alike to label frank periods of depression as "anemia," "malnutrition," etc. Further, it is quite likely that some of the deaths in children involving guns and hanging are not accidental. Relatives are notoriously skeptical of suicidal possibilities in depressed patients, and this seems especially true where children are concerned. Part of the routine care for a child injured in some suspicious manner would include discreet questioning by the physician with regard to the mood, stability of personality structure, etc. of his youthful patient.

At times, development of serious depression in children may represent a warning symptom, with subsequent development of full-blown psychotic illness, often schizophrenic. In addition, there are many reported instances of first episodes of a manic-depressive illness which began in early childhood. The authors have cared for a patient with a clear-cut manic-depressive illness who sustained his first depressive episode when he was eight years old. In this instance, and fairly often in a manic-depressive illness, there is a strong family history of serious emotional illness.

Not all instances of depression and suicidal gesturing in children represent psychotic illness. Some morose and unhappy youngsters, seemingly more often boys than girls, manifest their dissatisfaction and unhappiness about problems within the family in this fashion.

In general, these symptoms in a child are so antithetic to the usual patterns of childhood growth and development that consultation in a child psychiatric facility would usually seem to be indicated. In recent years a period of steroid therapy has occasionally been followed by the precipitation of a psychotic state in the treated child.

Late Adolescent and Early Adult Life: Depression and suicidal gesturing in late adolescence and early adult life present a complex diagnostic situation. For many people these are years fraught with great difficulties. Young people may be called upon for the first time in their lives to assume responsibility for their own support, to live independently of their parents, to fulfill military obligations, and to embark upon heterosexual relationships. Many of the episodes of depression and/or suicidal gesture occurring during this period of life represent the expression of frustration or resentment by generally unstable and immature young people. Many of the suicidal gestures within this age group are characterized by a scratch on the dorsum of the hand or an overdose of five aspirin tablets. Frequently there is some accompanying hyperaggressive reaction in association with alcohol, or some histrionic note or threat. Very frequently this histrionic element is marked, and there may be some immediate and specific precipitant, such as a rejection

in love, loss of a job, or threat of some punishment. In a military setting this kind of suicidal gesturing is relatively frequent, and such gestures often follow some minor punishment, the refusal of a commanding officer to grant a leave, rejection via the mails from a girl back home, etc. *Although accidents do happen*, these episodes are often marked by much commotion and relatively little damage. The suicidal gesture sometimes calls attention to a difficult situation of temporary nature. Even in those instances in which the histrionic elements seem predominant, hospitalization may have a definite place, and may do much to discourage further such gestures. In some larger cities, all patients who make suicidal attempts are hospitalized for psychiatric evaluation. Where this does not seem desirable or feasible, the physician must be guided by the patient's attitude and behavior while he is under treatment. In many instances, counseling with the patient and his family, brief hospitalization, and seeing the patient as an outpatient at intervals for a time may be all that is necessary. However, if during the time the patient is under treatment he seems continuously depressed or preoccupied, or expresses delusional or suicidal ideas, hospitalization becomes mandatory.

Unfortunately, not all instances of depression and suicidal gesture occurring in late adolescence and early adult life are manifestations of impulsive and immature personality. As indicated earlier, manic-depressive illness can begin at a very early age, and a significant number of such illnesses have begun by early adult life. It is also important to recall that many schizophrenic illnesses begin during these years. Schizophrenia was originally called dementia praecox, because it was felt, incorrectly, that this illness began inevitably during youthful years. Other symptoms of impending schizophrenic illness include extreme withdrawal, bizarre preoccupation with somatic worries, intense religious or philosophic preoccupation, inappropriate affect and/or evidences of hallucination, delusions, etc.

In summary, suicidal gestures and depression in adolescents and young adults may reflect quite differing kinds of emotional illnesses. In the main, such suicidal gestures will be made by unstable and immature young people, and in the vast majority of instances there is no great threat to life. Where the problem is primarily one of immaturity, impulsiveness and some acute situational problem, relatively simple therapeutic measures may be adequate. On the other hand, illness of psychotic proportion in this age group may also be heralded by depression or suicidal gesture. It is important to remember that, even in instances where histrionic elements predominate, accidents can happen, and serious injuries have been induced by miscalculation.

Depression in Older Adults: Failure to evaluate correctly a depressive illness in an older adult is one of the errors most frequently made in medical practice. This is especially important since the older person subject to depressive illness constitutes a great suicidal risk. No psychiatrist practices his profession for long without having instances where he miscalculates the

severity of depression in his patient, at times with fatal outcome. Even when the diagnosis is clear or the experience of the clinician is great, the correct decision as to what to do with a given depressed patient at a given time is one of the most difficult in all of psychiatric medicine. In general, in nonpsychiatric medical practice, there is a widespread inclination to underestimate the gravity of the patient's illness. Although some older adults have failed to outgrow the immaturity and instability of their adolescence and, like the adolescent, make histrionic suicidal gestures, their number is relatively small. Suicidal threat and/or gesture by a mature adult or older person should always warrant serious medical consideration.

As has been indicated above, these patients rarely present themselves to the physician saying, "I am depressed and life is not worth while." Much more frequently, the patient presents with somatic complaints. These complaints run the gamut of bodily illness. Difficulty with sleep is, however, an especially important clue with regard to depression. Often even very large quantities of sedatives provide sleep for only a few hours for the patient developing serious depression. Such patients are often on a constant quest for more sedation. Another common characteristic of the depressed patient in the older age group is a disproportionate concern about some aspect of his current life situation. This concern may have no real basis in fact. Such a patient, because of the intensity of his feelings, is often most convincing. Occasionally a patient may become delusionally despondent about imagined infidelity by his spouse. Occasionally, too, otherwise highly intelligent families have been split when the younger members believe a delusion about one or the other of the parents. Patients subject to this kind of illness are often in difficulty with regard to business or professional decisions, and there have been instances of profitable businesses sold for a fraction of their worth because of the owner's delusional feeling that life, and his business, were worthless.

Since the patient may not openly complain of depression or suicidal intention, the physician must himself be responsible for eliciting details of the patient's illness. Where the history, family history, symptoms or the patient's manner suggests depressive illness, the physician will want answers to many questions: How is the patient sleeping? How have his spirits been lately? How are his spirits now as compared with, say, six months ago? How does his future look? Has he felt bad enough that life did not seem worth while? Has he felt bad enough that he has even considered hurting himself? For each patient and for each doctor the manner of asking and answering these questions will be different, but they should be asked.

"Involutional Melancholia" and "Senile Depression": Some textbooks of psychiatry devote considerable space to a discussion of so-called "involutional melancholia," "senile depression," and perhaps a number of other subcategories of depressive illness occurring in older adults. In the authors' experience, these depressive reactions show no essential difference, sympto-

matically, dynamically, and in regard to general prognosis of depressive symptoms, from those described above under the heading of "Older Age Groups." At times, patients with very substantial amounts of organic brain damage who are also very depressed have responded to convulsive therapy by a lifting of their depression. Of course, the manifestations of organic brain damage in such patients remain. During the later years of life, people must face indisputable evidence of the loss of very important functions. Classically, this is also a time to take stock of one's life achievements, to look backward and to appraise what one has accomplished as compared with the ideals and aims one set out to achieve. This can be a most taxing undertaking.

MANAGEMENT OF THE OLDER DEPRESSED PATIENT

In an illness with the diverse characteristics of depression in older adults, simple management formulae cannot be uniformly applied. A nonpsychiatric physician faced with the problem of a specific patient who is depressed may elect to undertake a trial of treatment under his own supervision, may recommend psychiatric consultation, or may make immediate arrangements for hospitalization in a facility accustomed to dealing with depressed patients. The following suggestions are offered as a general guide for the management of depressed older individuals:

1. The physician should attempt to convey to his patient that he understands how badly the latter feels. A sense of isolation is very dangerous for the depressed person. The physician may want to remark: "I know it is hard for the people around you to understand how badly you feel, and I know it is hard for you to believe that you can be helped. You will have to try to realize that there is help for this kind of illness."
2. If the physician elects to embark upon a trial of medical management of a depressed patient, it may be worth while to consider the use of one of the newer antidepressant medications. When depression seems profound, Marsilid, 150 mg. per day for four days, followed by 50 mg. per day for a period of from two to four weeks, may be prescribed. Pyridoxine in a dosage of 10 to 25 mg. daily may be given along with Marsilid as a possible prophylactic medication. Toxic reactions to Marsilid have included peripheral neuropathy, delirium, blood dyscrasia and liver toxicity. In the authors' experience, the usual tranquilizing agents rarely provide relief from the depressive tones of this illness.
3. In no case should the patient leave the physician's office without being given a definite return appointment. Because of the sleeplessness and agitation usual in this condition, there is a timeless quality present, and the patient should not be left for a long period to his own devices.
4. The physician should not prescribe large doses of medicine of any sort, especially sedatives. Large amounts of barbiturates or tranquilizers make potent suicidal weapons. Also, having the patient return at least once

every week for refills of medicine represents a fine way to guarantee sustained medical observation.

5. If hospitalization seems indicated, it may be wise to avoid placing the patient in a small, nonpsychiatric hospital. There are many dangers implicit in hospitalizing depressed patients in facilities unaccustomed to dealing with this kind of illness.

6. If the physician waits until the depressed patient's suicidal intentions are abundantly clear, he may have waited too long.

7. It is well to remember that certain physical illnesses are notoriously depressant in effect—pancreatic disease, i.e., chronic pancreatitis or carcinoma of the body of the pancreas, brain tumor, and toxic states in association with bromides, barbiturates and *Rauwolfia* may produce a depressive picture.

8. Often when the family physician has feared the consequences of suggesting psychiatric consultation, the patient and his family actually appreciate such referral.

THE ROLE OF CONVULSIVE THERAPY

One of the most distressing aspects of "electrical shock" therapy is its name. Such therapy might better be called "electrical sleep" therapy. Ordinarily, in convulsive therapy, the patient will experience sleep rather than any kind of "shock." Where it is indicated, there is no more gratifying therapeutic régime in medicine than the use of convulsive therapy in depression. In expert hands, convulsive therapy is remarkably safe, painless, and therapeutically rewarding—many thousands of treatments are given without serious morbidity or mortality. Usually, patients receiving such therapy belong on a closed psychiatric ward, because of the transient impairment of memory which may be produced. Ordinarily, memory loss diminishes rapidly following the termination of treatment. Although convulsive therapy is of little or no value in the neuroses, and of only moderate value in the treatment of schizophrenic illness, it is the treatment of choice in many older depressed individuals. These illnesses in older individuals have a tendency to recur, and some patients will require repeated courses of convulsive therapy. These recurrences may develop after intervals of from less than a year to periods of more than 15 or 20 years. In addition, some patients with especially refractory illness or recurring relapses have seemed to derive benefit from a "maintenance" régime of convulsive therapy, with treatments given on a once-weekly or once-monthly basis. If a depressive illness is of sufficient magnitude to warrant convulsive therapy, psychiatric referral is clearly indicated.

SUMMARIO IN INTERLINGUA

Le evalutation del paciente deprime es un del plus difficile problemas in le practica medical. Medicos in omne specialitates se trova de tempore a tempore confrontate con le necessitate de evalutar le grado de depression presente in un certe paciente e de estimar le periculo de suicidio. Evidentemente, un miscalculation diagnostic in iste tipo de situation pote resultar in un catastrope.

Le autores ha interprendite un revista del problemas sublivate per le paciente deprimeite a intentiones suicidal. Le depression experientiate phenomenologicamente per le paciente es describite como un stato discouragante e frequentemente pervasive ab le qual le paciente non vide ulle escappatoria. Es sublineate le facto que le intensitate e le realitate subjective del despero del paciente deprimeite pote esser multo plus grande que simile emotiones in pacientes qui suffe incurabilmente de un morbo somatic.

Multe deprimeite pacientes se presenta al medico con gravamines attribuibile a un morbo somatic. In casos in que le depression es assi associate con un morbo somatic, le medico tende a subestimar le importanta relative del depression in le symptomatologia general. Iste problema diagnostic es specialmente marcate in pacientes del grupplos de etate plus avantiata ubi il es natural attribuer le symptomas del depression a condicioneis del tipo de hypertension, arthritis, disordines functional del intestinos, "insomnia", etc.

Le question del factores etiologic in le stato de depression es considerate ab le punto de vista psychodynamic e ab le punto de vista psychobiologic.

Es discutite le importanta del etate del paciente al tempore del declaration del depression como factor diagnostic e etiologic in le evalutation del depression e del intention suicidal. Depression e intention suicidal es observate a omne stadios del vita, ab le prime pueritia usque al alte vetusssa. Tamen, il existe importante differentias in le signification del symptomatologia depressive occurrente a varie periodos del vita.

Le autores sublinea le extense tendentia in le practica medical de subestimar le severitate del depression, specialmente del depression que occurs in adultos matur o vetulante.

Le thema del therapia de pacientes deprimeite e suicidalmente intentionate es discutite. Le importantia del interesse del medico, de su continue attention, e de un intervention opportun es sublineate.

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EXPERIENCES WITH THE "VIGOROUS DIAGNOSTIC APPROACH" TO UPPER GASTRO-INTESTINAL HEMORRHAGE *

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THE unfortunate patient who is bleeding from undetected esophageal varices and is subjected to needless abdominal exploration because his doctor suspects duodenal ulcer as the cause gets little comfort from statistics. While it is perfectly true that ulcer accounts for the majority of serious upper gastrointestinal bleeding, there is ample evidence of the practical possibility of hemorrhage from other lesions.¹⁻¹³ Though these may be less common statistically, they still are important numerically, and may be vital to the individual patient who has one.

It may seem heretical, but the reliability of the history, past history and physical examination in pointing out the proper diagnosis in every case of gastrointestinal hemorrhage must be seriously questioned. Not only may those traditional diagnostic bulwarks fail us, but one may also be misled dangerously by them. Of particularly pertinent significance is Palmer's¹⁰ observation that, of those patients in his experience with proved past histories of potential bleeding lesions such as ulcer, 50% turned out to be hemorrhaging from some *other* source. The patient with cirrhosis of the liver has received special attention in this regard. Several authors¹¹⁻¹⁴ have listed an impressive number of possible bleeding sources in such patients other than esophageal varices.

These pitfalls can be avoided by proper application of diagnostic technics early in the evaluation of the bleeding patient. Barium contrast x-ray has been used with various modifications designed to minimize the manipulation and palpation usually employed.¹⁵⁻¹⁶ Recently, even those precautions have been relaxed by some in selected cases.^{1, 10, 17} Esophagoscopy and gastroscopy are valuable in that direct visualization of the offending lesion may be possible. Equally important, the *absence* of a bleeding source above the diaphragm may be confirmed by esophagoscopy.

As long ago as 1925, Chevalier Jackson recognized this problem. In a paper entitled "Hematemesis: A Plea for Objective Methods of Diagnosis,"¹⁸ he cited nine cases where esophagoscopy, sometimes performed during active hemorrhage, revealed lesions not discoverable by history and physical examination, and in some cases not even by x-ray.

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Since that time others have advocated the early use of esophagoscopy, gastroscopy and x-ray, singly and in various combinations, in the evaluation of the bleeding patient.^{1, 15, 17, 19-25} This is a radical departure from the philosophy that even palpation of the abdomen and restoration of blood volume must be avoided because of the supposed danger of intensifying the bleeding.

Those who advocate peroral endoscopy as part of this technic are fully aware of the dangers inherent in those procedures. It is their philosophy that lack of a diagnosis, and consequent misdirection of therapy, are far more dangerous than the skilful application of a bold diagnostic attack. The patient bleeding from esophagitis or esophageal varices will thus not be subjected to needless and, under the circumstances, doubly dangerous abdominal exploration. Nor will esophageal balloon tamponade be employed, even as a trial, in a patient with cirrhosis and esophageal varices who happens to be bleeding from an undetected duodenal ulcer.

PATIENTS

In the last two and one-half years, 85 patients have been admitted to Brooke Army Hospital because of serious upper gastrointestinal hemorrhage. No attempt was made to adhere to any strict quantitative criteria for the diagnosis of "massive gastrointestinal hemorrhage." The basic requirement for inclusion of a patient in this series was continuation of active bleeding after admission to the hospital, indicating a strong possibility that specific measures might be needed to control the hemorrhage. These patients were all active duty or retired military personnel and their families, and Veterans Administration beneficiaries. Eighty of them were men and five were women. Their ages ranged from 22 to 79 years, the majority (68%) being between 40 and 60. Forty-five per cent were over 50 years of age. Eighty-two of the 85 were white. Most of the patients were admitted to the Recovery Ward of the Surgical Service; management was under the direction of a team consisting of the gastroenterologist, surgeon and radiologist. Nearly every patient received at least 1,000 ml. of whole blood during the first six to 12 hours because of varying degrees of shock or anemia. In each instance, careful history and physical examination were carried out and, if available, old x-rays and hospital records were reviewed. Based upon these, an "initial impression" was clearly stated and recorded in the patient's chart. Active therapy, however, other than general resuscitative measures, depended upon the results of the early use of diagnostic technics.

METHOD

"The vigorous diagnostic approach" employed in the evaluation of these patients is similar to that described elsewhere in detail.^{1, 10} Briefly, this requires that efforts first be directed toward resuscitation, if it is necessary,

employing the usual measures. As soon as the patient's condition permits, gastric lavage with ice-water using a French 30 Ewald tube is carried out, followed at once by esophagoscopy and gastroscopy, and then a barium-contrast upper gastrointestinal x-ray. Patients are usually prepared for endoscopy with small doses of Demerol and atropine, but local anesthesia of the pharynx is seldom necessary, nor is it usually employed. Thus, the patient may swallow barium sulfate suspension safely, without the necessity of waiting for the return of pharyngeal sensation. The radiologist employs whatever maneuvers are needed to carry out his study, the only limitations being that occasionally a patient must be examined lying down. Esophagoscopy and gastroscopy are usually carried out on the litter upon which the patient is brought to the endoscopy clinic, and upon which he is then transported to the fluoroscopy room. In several instances the patient's condition prohibited transportation, and the endoscopic examinations were carried out in bed on the ward. It is possible to continue the administration of blood transfusions and other resuscitative fluids during the various diagnostic procedures.

Ideally, none of these procedures should be omitted, nor should the order in which they are carried out be varied. Exigencies of the moment dictated departure from the pattern in several cases, however. In two instances unsuspected hiatus hernia would not permit easy passage of the Ewald tube and the important gastric lavage was abandoned; esophagoscopy or x-ray made the diagnosis, and gastroscopy was not attempted. Neither esophagoscopy nor gastroscopy was carried out in four of the 85 patients—in one instance because an old mandibular fracture prevented the patient from opening his mouth sufficiently wide, in another because of anatomic abnormality of the cervical spine, and in two because of inability to coöperate. Gastroscopy was performed in only 28 of the patients. In some cases in which it was omitted the positive identification at esophagoscopy of hemorrhage from an esophageal lesion precluded gastroscopy. A completely normal esophagoscopy was also frequently considered to be sufficient evidence that the bleeding was from below the diaphragm, and it was felt in these cases that gastroscopy would add little information. This is admittedly a calculated risk, since some instances of gastric varices and diffuse hemorrhagic gastritis might have been missed. The x-ray was omitted in 12 instances either because that examination had been done within a few days prior to the hemorrhage or because the severity of the hemorrhage and the patient's condition dictated immediate laparotomy, the esophagus having been found to be normal at esophagoscopy.

RESULTS

No patient was injured, either by endoscopic accident or intensification of the hemorrhage, as a result of these early diagnostic studies. Indeed, just as in Palmer's experience,^{1,10} ice-water lavage stopped or significantly reduced the rate of bleeding in the majority of instances, whatever its source.

Table 1 summarizes the over-all experience with this group of cases. As can be seen, the initial "impression" was correct in only 48 (or 56.4%) of the 85 cases studied. In 25 instances (or 29.4%) it was incorrect, and in 12 (or 14.2%) no definite source of the bleeding could be demonstrated, in some cases even at laparotomy.

TABLE 1

| Initial Impression | Duo-denal Ulcer | Esoph. Varices | Gastric Ulcer | Marginal Ulcer | Hiatus Hernia | Ca Stomach | Esophagitis | Mallory-Weiss | No. | % |
|---------------------|-----------------|----------------|---------------|----------------|---------------|------------|-------------|---------------|-----|------|
| No. times made | 60 | 10 | 4 | 4 | 3 | 2 | 1 | 1 | 85 | 100 |
| Correct | 40 | 3 | 3 | 1 | 1 | 0 | 0 | 0 | 48 | 56.4 |
| Wrong | 13 | 4 | 1 | 2 | 1 | 2 | 1 | 1 | 25 | 29.4 |
| No diagnosis proved | 7 | 3 | 0 | 1 | 1 | 0 | 0 | 0 | 12 | 14.2 |

Of the 25 cases in which the initial impression was incorrect, not all would have been injured by direction of specific measures against the suspected cause. For example, if abdominal laparotomy becomes necessary, it is the correct approach to a bleeding gastric ulcer or carcinoma in a patient believed initially to be hemorrhaging from a duodenal ulcer.

TABLE 2

| Case No. | Age | Sex | Initial Impression | Final Diagnosis |
|----------|-----|-----|------------------------|---------------------------------|
| 1 | 55 | M | Hiatus hernia | Gastric lymphoma |
| 2 | 59 | M | Hiatus hernia | Duodenal ulcer |
| 3 | 62 | M | Duodenal ulcer | Esophagitis, hiatus hernia |
| 4 | 57 | M | Duodenal ulcer | Esophageal ulcer, hiatus hernia |
| 5 | 33 | M | Duodenal ulcer | Esophageal varices |
| 6 | 43 | M | Esophageal varices | Duodenal ulcer |
| 7 | 46 | M | Duodenal ulcer | Mallory-Weiss syndrome |
| 8 | 61 | M | Mallory-Weiss syndrome | Duodenal ulcer |
| 9 | 62 | M | Gastric carcinoma | Esophageal varices |
| 10 | 66 | M | Esophageal varices | Gastric carcinoma |
| 11 | 74 | F | Gastric ulcer | Esophageal ulcer |

In 11 instances (12.9% of the total), however, the bleeding proved to be from such unexpected sources that treatment directed at the suspected cause would have been totally ineffective or even harmful (table 2).

CASE REPORTS

Case 1. A recurrence of a previously repaired hiatus hernia was initially suspected as the source of hemorrhage in a 55 year old white man. Esophagoscopy was normal, however. At surgery, the bleeding was found to be from ulcerated lymphosarcoma of the stomach. Subtotal gastrectomy successfully controlled the hemorrhage. Radiation therapy was administered and the patient was well 24 months later.

Case 2. A 59 year old man was known to have a hiatus hernia. That was suspected as the source of hemorrhage until esophagoscopy revealed neither esophagitis nor gastritis of the herniated gastric pouch. An upper gastrointestinal series demonstrated a previously undetected duodenal ulcer. Management was conservative.

Case 3. Based upon history alone, a 62 year old man was suspected of hemorrhaging from a duodenal ulcer. Esophagoscopy revealed severe esophagitis above a totally unsuspected hiatus hernia, and x-ray showed a possible ulcer in the hernia pouch. Conservative treatment was successful.

Case 4. A 10 year history of burning epigastric pain and intermittent mild hemorrhage in a 57 year old man suggested duodenal ulcer as the source of the current massive hemorrhage. The history of heavy alcohol ingestion raised the possibility of portal cirrhosis and esophageal varices. The first clue to the true diagnosis came when the Ewald tube would not pass easily through the cardia, and gastric lavage was necessarily abandoned. Esophagoscopy was attempted anyhow, and was sufficiently satisfactory to rule out esophageal varices. The gastrointestinal series revealed hiatus hernia and esophageal ulcer with partial stricture. Despite this information, which permitted successful control of the hemorrhage at surgery, the patient died 12 hours later in irreversible shock.

Case 5. Painless duodenal ulcer was the suspected source of hemorrhage in a 33 year old man who had neither hepatosplenomegaly nor other evidence of portal hypertension. Esophagoscopy revealed hemorrhage from large esophageal varices. Balloon tamponade was successful, and later a portacaval anastomosis was performed, with excellent results.

Case 6. A past history of beriberi, scurvy and recurring episodes of jaundice while a prisoner of war in the Philippines during World War II prompted an initial impression of postnecrotic cirrhosis and esophageal varices in a 43 year old veteran. Esophagoscopy was normal, however. A duodenal ulcer was found on a gastrointestinal series; ulcer symptoms had been minimal and insignificant. Conservative management was successful.

Case 7. A 46 year old man with a long history of duodenal ulcer was found at esophagoscopy to have a laceration across the esophagogastric junction (Mallory-Weiss syndrome).²⁰ The ulcer had caused partial pyloric obstruction but was not believed to be the source of hemorrhage. Conservative management controlled the acute situation; subtotal gastrectomy was performed later.

Case 8. Mallory-Weiss syndrome was suggested by the history given by the 61 year old man. Esophagoscopic and gastroscopic search for the laceration was negative, and an upper gastrointestinal series revealed a duodenal ulcer. Conservative management successfully controlled the acute episode; partial gastrectomy was carried out later, with good results.

Case 9. A long history of postprandial abdominal pain, vomiting, weight loss and hepatomegaly prompted an admission impression of gastric carcinoma as the bleeding source in a 62 year old farmer. Hemorrhage from esophageal varices was diagnosed with confidence at esophagoscopy and controlled by balloon tamponade. Death was due to hepatic coma 10 days later; autopsy revealed severe portal cirrhosis.

Case 10. A 66 year old white man was hospitalized because of anorexia, weight loss, jaundice and hepatomegaly. Hemorrhage began 12 hours after admission, and esophageal varices were considered to be the most likely source. Esophagoscopy was normal, but gastroscopy revealed an ulcerated gastric carcinoma, also demonstrable later on x-ray. The bleeding stopped spontaneously; the patient died six weeks later of generalized carcinomatosis.

Case 11. A 74 year old woman, admitted from a nursing home, had a history and past history suggesting gastric ulcer as the source of her hemorrhage. Severe kyphoscoliosis prohibited esophagoscopic visualization of the distal one third of the

esophagus, but x-ray revealed an ulcer there; the stomach was normal. The bleeding stopped with conservative treatment.

In one other case²⁷ a source of bleeding ordinarily considered to be within the diagnostic range of esophagoscopy and gastroscopy was missed:

Case 12. Abdominal exploration was carried out in a 26 year old man after esophagoscopy and x-ray were interpreted as normal. Duodenal ulcer was considered to be the most likely source of the hemorrhage, but bleeding was noted from the region of the cardia; a 2 cm. laceration was identified as its source and was easily sutured. This example of the Mallory-Weiss syndrome²⁸ might have responded to balloon tamponade had it been used, and laparotomy might thus have been avoided. Fortunately, the eventual outcome was a happy one.

In 12 of the 85 patients (14.2%), no definite source of hemorrhage was ever found, even in three instances of the 12 where abdominal exploration was carried out. In all 12, however, the "vigorous diagnostic approach" gave complete assurance that the esophagus was *not* the source of the hemorrhage, so that, had it been indicated by continued bleeding, abdominal exploration could have been carried out in the other nine patients without fear of misdirection.

Deaths: Hemorrhage alone was considered to be directly responsible for the deaths of four patients (4.7%) of this group. One of these is described above (case 4). Two others died on the operating table during heroic efforts to halt bleeding from gastric and postbulbar duodenal ulcers, respectively. Both patients were elderly men with marked, generalized arteriosclerosis. A fourth patient, bleeding from esophageal varices secondary to severe portal cirrhosis, died when his Sengstaken-Blakemore tube, presumed to be well placed and functioning, was suddenly displaced by a recurrence of massive hematemesis.

Nine others also died, but in each instance the "vigorous diagnostic approach" had permitted specific application of measures which successfully controlled the bleeding, and death was due to other causes indirectly related to the hemorrhage. For example, in one case death was due to fulminant peritonitis following perforation of a gangrenous duodenal stump; subtotal gastrectomy had successfully controlled severe, continuous hemorrhage six days earlier. The other deaths occurred from one to 21 weeks after cessation of bleeding, and were caused by various conditions, such as hepatic coma, generalized carcinomatosis and, in one instance, myocardial infarction three weeks later.

In every patient who died, the "vigorous diagnostic approach" had permitted optimal management of the initial hemorrhage.

DISCUSSION

A precise statistical evaluation of the over-all results of this study will not be attempted. The variable responses of patients even to known amounts

of blood loss, and the unmeasurable influence of other diseases, especially cardiovascular and hepatic, introduce too many uncontrollable factors. Equally important is the lack of a personally observed control group managed by methods other than the "vigorous diagnostic approach."

The chief value of this study is to be found in examination of the 11 cases where the "vigorous diagnostic approach" revealed serious errors in the initial impression. Thus, in those patients requiring more than conservative management, specific measures were directed with confidence. It was felt that even those patients who died had received the greatest possible chance for survival. The mortality rate of 4.7% probably would have been significantly higher without the "vigorous diagnostic approach," and certainly several needless major surgical procedures would have been performed.

No claim is made that the "vigorous diagnostic approach" permitted a positive diagnosis of the precise source of bleeding in every case in this series. However, a negative report is just as valuable in some instances as a positive one. For example, assurance that the patient is *not* bleeding from esophageal varices is invaluable information if continued hemorrhage demands hemostatic measures—completely confident exclusion of varices is impossible without esophagoscopy.²⁸ A trial of esophageal balloon tamponade may be made, but valuable time and blood may be lost if the hemorrhage is from a duodenal ulcer with an arteriosclerotic vessel in its base.

Those who advocate less vigorous diagnostic methods in the evaluation of these patients frequently object to the "trauma" of peroral endoscopy. Once again it is pointed out that, in this series, no patient was injured either by endoscopic accident or by aggravation of his hemorrhage. In only two instances did lack of cooperation by a patient prevent endoscopy. In every case the procedures and the important reasons for performing them were carefully explained to the patient. Understandably apprehensive, the patient was thus assured that everything possible was being done in his behalf. Esophagoscopy and gastroscopy were then accomplished in most cases with little difficulty, especially when it is recalled that local anesthesia of the pharynx was seldom employed.

Those practitioners of esophagoscopy and gastroscopy who advocate a "vigorous diagnostic approach" do not do so merely to show that those procedures can be done under difficult conditions. Rather, it is because of dissatisfaction with diagnostic and hence therapeutic results, when reliance is placed solely upon the history and physical examination.

SUMMARY

Eighty-five patients hospitalized because of serious upper gastrointestinal hemorrhage were evaluated by the "vigorous diagnostic approach."¹ This application of diagnostic technics early in the course of the bleeding showed that the initial impression, based upon history and physical examination, was

correct in 48 (56.4%) of the cases. The admission diagnosis was incorrect in 25 of the cases. In 11 of those (or 12.9% of the total), the source of hemorrhage turned out to be from such unexpected sources that direction of therapy at the suspected cause would have been useless or even harmful.

It is believed that the mortality directly attributable to hemorrhage (4.7%) would have been considerably higher if treatment had been directed at those diagnoses based upon history and physical examination alone.

SUMMARIO IN INTERLINGUA

Octanta-cinque patientes con sever hemorrhagia supero-gastrointestinal esseva evalutate immediatamente post lor admission al hospital per medio de esophagoscopya e radiographia a contrasto per barium. Gastroscopia esseva etiam effectuate in multes del casos. Un lavage gastric preliminari, effectuate per medio de aqua glaciante e un tubo de Ewald (calibre F 30), resultava in un relentation del hemorrhagia in le majoritate del casos, sin reguardo al origine de illo. Le elimination de sanguine accumulate facilitava le measuras diagnostic.

Le uso de iste "vigorose methodologia diagnostic" es considerate como essential in le evalutation de tal patientes, proque le scrutinio le plus meticulose del historia del casos individual e le examine physic sin altere measuras produceva le correcte diagnose in solmente 48 del 85 patientes (i.e. in 56,4%). In 25 del casos (29,4%), le diagnose basate solmente super le historia e le examine physic esseva incorrecte. In 12 del casos (14,2%), nulle definite diagnose poteva esser estableite, ben que le gruppo includeva tres patientes subjicite a laparotomia. Tamen, in omne iste 12 casos, esophagoscopya excludeva convincentemente le possibilitate de un fonte esophagee del sanguination. Quanto al gruppo de 25 casos in que le diagnose per historia e examine physic sol esseva erronee, in 11 de illos le "vigorose methodologia diagnostic" revelava que le fonte del hemorrhagia esseva talmente inexpectate que un therapia specific attaccante le causa suspecte haberea essite completelymente futile e possibilmente nocive. Assi il esseva trovate que duo subjectos con previamente demonstrata hernia de hiato sanguinava ab ulcere duodenal e lymphoma gastric, respectivemente. In quatro patientes con forte indicios clinic de ulcere duodenal como fonte de lor hemorrhagia, il esseva constatare que illes sanguinava ab (1) esophagitis con hernia de hiato, (2) ulcere esophagee secundari a hernia de hiato, (3) varices esophagee, e (4) le syndrome de Mallory-Weiss, i.e. laceration del junction esophagogastric in consequentia de repetitive vomito violente. In un altere paciente, in qui le indicios clinic supportava un diagnose de syndrome de Mallory-Weiss, le presentia de un previamente non suspecte ulcere duodenal esseva constatare. Un paciente con definite signos clinic de hypertension portal e varices esophagee como fonte del hemorrhagia sanguinava de facto ab un ulcere duodenal. Un secunde paciente con plus o minus le mesme aspecto clinic sanguinava ab un carcinoma gastric. Del altere latere, un paciente in qui le aspecto clinic supportava le suspicion de sanguination ab un carcinoma esseva recognoscite como sanguinante ab previamente non evidentiate varices de esophago. In un femina de etate avantiata con un historia de ulceras gastric e symptomas indicante un recurrentia, il esseva trovate que le fonte del sanguination esseva de facto un ulcere esophagee.

Nulle del patientes evalutate per le "vigorose methodologia diagnostic" esseva vulnerata per un accidente endoscopic, e nulle suffreva un aggravation de su hemorrhagia. Quattro del 85 patientes (4,7%) moriva in consequentia directe de lor hemorrhagia. In omne iste casos, le "vigorose methodologia diagnostic" habeva resultate in le estableimento del correcte diagnose, sed le morte occurreva in despecto del institution del melior tractamento possibile. Le assertion pare justificate que le mor-

talitate habere essite plus que 4,7% sin le "vigorose methodologia diagnostic." In omne caso, plure superflue interventiones chirurgic esseva evitate.

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THE MUCOCUTANEOUS LESIONS OF REITER'S SYNDROME *

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IN recent years we have observed a number of patients with Reiter's syndrome. Although the triad of urethritis, conjunctivitis and arthritis is now rather well known, the high incidence of mucocutaneous lesions is not generally appreciated. These lesions, in our experience, are practically diagnostic, and occur very frequently in the endemic or venereal type of the disease. In fact, this type of Reiter's syndrome might better be considered a tetrad, consisting in its complete form of urethritis, conjunctivitis, arthritis and mucocutaneous lesions. It is the purpose of this paper to point out the character and frequency of the various mucocutaneous lesions, and also to emphasize their role in establishing a definite diagnosis. This is important, since Reiter's syndrome follows a fairly characteristic course, is self-limiting, and carries a much better prognosis than do most other arthritides.

The incidence of mucocutaneous lesions in 38 patients with Reiter's syndrome treated during a 10-year period at the Hines Veterans Administration Hospital was found to be 80%, a figure higher than that reported in most series. Weinberger, Dienes and Bauer noted circinate ulcers on the glans penis in six of 15 patients, and hyperkeratotic lesions on the soles and palms of two patients, and mention that superficial erosions of the buccal mucosa also occurred.¹ Paronen, in his large series of the epidemic or dysenteric type, reported mucous membrane lesions of the penis in 111 of 344 patients, stomatitis in nine patients, and skin lesions in 10 patients. Two of the latter had hyperkeratotic lesions, or "rupia."² Parakeratotic balanitis, or balanitis circinata, was reported in 39 of Harkness' 115 patients. "Septic" mouth lesions were noted in many of his patients, but in only six were superficial ulcers of the buccal and palatal mucosa observed. He stated that many oral lesions were undoubtedly overlooked.³ On the other hand, all 23 patients reported by Hall and Finegold had mucocutaneous lesions. There were involvement of the glans penis or prepuce in 18, lesions of the oral cavity in 11, and similar lesions on the tongue in five patients. Five of the 23 also had hyperkeratotic skin lesions.⁴

Our criteria for Reiter's syndrome were strict, since we wished to study only patients in whom we felt certain of the diagnosis. These criteria con-

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sisted, in the majority of patients, of the typical triad, urethritis, conjunctivitis and arthritis, together with the proper temporal relationships and the typical self-limiting course without residual joint deformities. Urethritis was recognized in 35 of the 38 patients, and the other three had pyuria. Conjunctivitis was absent in only five. In all instances arthritis was the disabling component. It is recognized that there is difficulty in the documentation of urethritis or conjunctivitis in patients seen a number of weeks



FIG. 1. Balanitis circinata, perimeatal erosions and hyperkeratotic skin lesions on the thighs.

after onset of the illness. In such cases, mucocutaneous lesions which appear four to six weeks after appearance of the urethritis may be the factor which establishes a definite diagnosis. This was true in several instances. Patients with mild forms of the syndrome probably were not hospitalized, and those presenting only one component in addition to the arthritis would not meet our criteria.

In the group of 38 patients fulfilling strict criteria, mucous membranes of the genitalia were affected in 30; mucous membranes of the mouth,

pharynx and tongue were affected in 14 of these 30. The skin was affected in 11 of the group. In no instance was the skin alone involved, and in no patient were oral mucous membrane lesions an isolated finding.

Genital Lesions: Perimeatal erosions and balanitis circinata are probably of identical nature, and were present in all 30 of the 38 patients with mucosal lesions (figure 1). Twenty-three had both lesions; four of the remaining seven had perimeatal erosions, while the other three had balanitis circinata alone. The perimeatal lesions are superficial dark red erosions adjacent to, or partially to completely encircling, the external urinary meatus. They are painless, and are not covered by an exudate or membrane but occasionally by thin, loosely adherent, yellow to brown scales. The lesions of balanitis



FIG. 2. Painless erosions of buccal mucous membranes.

circinata are also superficial and painless, involve the foreskin and glans, especially the corona, and are also covered by thin brownish crusts or scales which are easily scraped off. Beneath the scales the mucosa is smooth, dark red and very slightly elevated. Bleeding does not occur. When ointments have been used the lesions appear to be smooth, dark red and clean. The surrounding mucosa or skin does not appear to be inflamed. Frequently the entire glans and foreskin may be reddened, though not painful. Associated maculopapular lesions, varying from 2 to 5 mm. in diameter, are sometimes seen on the glans. These are painless, dark red and slightly elevated, and are often covered by thin scales but not by hard crusts. Possibly these lesions represent the mucous membrane equivalent of the hard, crusted hyperkeratotic lesions of the palms and soles (keratosis of Reiter's

syndrome). Occasionally deeper, nonpainful ulcers in the region of the frenum or on the shaft of the penis are seen. These have been termed "soft parakeratotic lesions."³

Buccal and Pharyngeal Lesions: Of the 30 patients with genital involvement, 14 had, in addition, painless lesions of the oral, pharyngeal or glossal mucous membranes (37% of the entire group). Others had diffuse injections of the palate and pharynx, and darker red mucosal areas which possibly represented a resolving phase of previous lesions; these were not considered to be characteristic. The typical lesions are dark red, slightly elevated, painless macules varying from 1 mm. to over 1 cm. in diameter (figure 2). They are not covered by an exudate or membrane, and are not

TABLE I
Oral and Pharyngeal Mucous Membrane Lesions

| Patient's* Number in Series | Buccal Mucosa | Gingiva and Alveolus | Palate | Tongue | Pharynx | Nose | Details and Location of Other Lesions |
|-----------------------------|---------------|----------------------|--------|--------|---------|------|--|
| 3 | — | — | + | — | — | — | |
| 5 | — | — | + | — | — | — | "Herpetiform." Small, elevated lesion. |
| 9 | + | + | + | — | + | — | Elevated dark red macular lesions. Up to 2 cm. in diameter. Painless. |
| 12 | — | — | + | + | + | — | |
| 14 | + | — | + | — | — | — | |
| 17 | + | + | + | — | — | — | |
| 21 | + | + | + | + | + | — | Nonpainful erosions, nasal mucosa. Nonpainful, reddened, slightly elevated lesions. Perianal lesions also. |
| 24 | + | + | + | + | + | — | Pharynx also diffusely injected. |
| 27 | — | — | + | — | — | — | |
| 28 | + | — | — | + | — | — | |
| 31 | + | + | + | + | + | — | Superficial painless erosions with diffuse redness. Nasal mucosal lesions. |
| 33 | + | + | + | — | — | — | |
| 35 | + | + | + | + | + | — | External auditory meatus and nasal mucosal lesions. Perianal lesions. |
| 36 | + | + | + | + | + | — | Nasal mucosal lesions. |

* All patients in this table had genital membrane lesions.

surrounded by an inflammatory zone. Since they are not tender, the patient is not aware of their presence, and they must be searched for to be identified. They occur on the buccal mucosa opposite the alveolar processes as well as on the palate, alveolar processes, pillars, pharynx and tongue. The palate is sometimes covered by multiple bright red purpuric spots from 1 to several millimeters in diameter. These later darken and coalesce. Manifestations vary in appearance, depending upon whether they are located on the hard or soft palate. Similar painless, superficial red erosions are seen on the tongue. None of them interferes with eating, thus differing from the painful oral lesions of Stevens-Johnson syndrome. Rarely the nasal mucosa, the anal and perianal region and the external auditory canals present

superficial painless, nonpruritic, diffuse reddened areas. In some of our earlier patients, mucous membrane lesions may have been overlooked.

The distribution of extragenital mucous membrane lesions in our 14 patients is shown in table 1. Since two patients were treated for single recurrences and another two for three episodes, our 14 patients had a total of 20 attacks. In only two instances were oral mucosal lesions absent.



FIG. 3. Keratodermia of Reiter's syndrome, showing distribution of the cone-shaped lesions on the weight-bearing area of the sole.

The same general areas were affected in patients experiencing multiple attacks.

Cutaneous Lesions: The keratosis of Reiter's syndrome, often called keratoderma blennorrhagica, occurred in 11 of the 30 patients with mucosal lesions, an incidence of 30% of our entire group of 38 patients. Nine presented hard nodular keratotic lesions, and two had soft parakeratotic patches.³ Like the mucous membrane lesions, the keratotic lesions usually

crop out from four to six weeks after the onset. In the early stage they most often are located on the weight-bearing surface of the ball of the foot. While these lesions appear to be small, red to yellowish brown cone-shaped vesicles or pustules, they are actually solid and firm on palpation (figure 3). Other groups appear over the lateral weight-bearing areas of the sole and heel. They become confluent and form thick, brownish black crusts which interfere somewhat with walking but are not painful. Often the skin between the toes becomes macerated and peels. Adjacent healthy skin does not appear to be inflamed, and there is no itching. After a few weeks the thickened hyperkeratotic crusts fall off, exposing nonsensitive new skin. Lesions may also be discrete and few in number, and the crusts sometimes do not project above the thick skin of the sole. Thick, crustlike formations

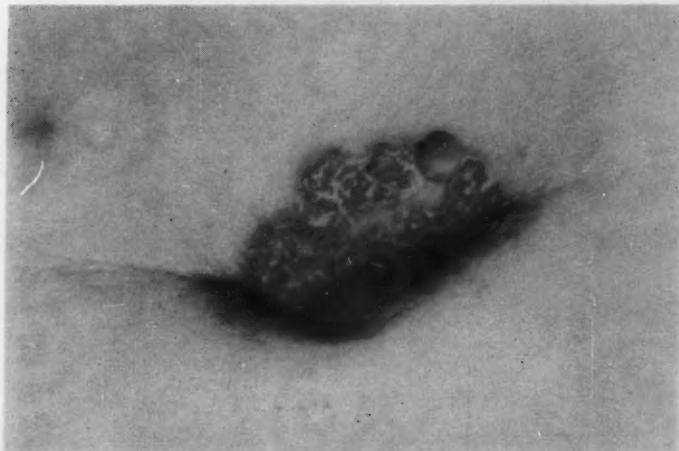


FIG. 4. Hyperkeratosis of the umbilicus.

up to 1 or 2 cm. in diameter may appear on the dorsum of the feet, on the legs or palms, or on the dorsum of the hands or the forearms. Crusting about the umbilicus (figure 4), at the scalp margin and in the scalp may also occur. Large blebs up to 5 cm. in diameter occasionally are seen on the soles of the feet.

The toenails and fingernails are affected in most patients, and there is loss of one or more nails in at least half of those having keratosis. The nails become discolored as dry, yellowish debris accumulates beneath the distal half. Later the entire nail is elevated by this material, turns dark brown or black, and eventually is shed (figure 5). The skin adjacent to the nail base and nail fold is also involved in the process. Sterile subungual abscesses may form. These lesions are not painful and do not itch. The clinical appearance resembles psoriasis. Ulcers of the shaft of the penis,

with little surrounding inflammation as well as diffuse scrotal erythema with seeping erosions, are occasionally noted. These are the soft "parakeratotic lesions."³ Diffuse generalized superficial dermatitis with desquamation occurs sometimes, but this is nonspecific and difficult to evaluate and differentiate from a drug reaction. Table 2 lists the type and distribution of



FIG. 5. Nail changes of Reiter's syndrome.

skin lesions. It can be seen that vesicle-like and pustule-like lesions and hard crusts were present in practically all; loss of nails occurred in six, and bullae of the soles in five. Cases 10 and 11 showed only soft lesions. In one of these patients multiple nails were affected, and eventually several were lost. In addition, a diffuse erythematous papular rash of the abdomen and hands was followed by desquamation. The other patient had soft para-

TABLE 2
Cutaneous Lesions of Reiter's Syndrome

| Patient's* Number in Series | Vesicle-like Lesions | Pustule-like Lesions | Hard Crusts | Nail Involvement | Loss of Nails | Subungual Abscesses | Umbilical Lesions | Scalp Crusts | Desquamation, Soles of Feet | Ulcers, Shaft, Penis | Scrotal Dermatitis | Bullae, Soles of Feet | Area of Desquamation of Trunk |
|-----------------------------|----------------------|----------------------|-------------|------------------|---------------|---------------------|-------------------|--------------|-----------------------------|----------------------|--------------------|-----------------------|-------------------------------|
| 1 | ++ | ++ | ++ | +++ | ++ | - | + | + | + | - | - | + | + |
| 2 | + | - | - | - | - | + | - | - | - | - | - | - | - |
| 3 | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 12 | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 13 | + | + | + | ++++ | +++ | + | + | + | + | + | + | + | + |
| 14 | + | + | + | ++++ | +++ | + | + | + | + | + | + | + | + |
| 20 | + | + | + | ++++ | +++ | + | + | + | + | + | + | + | + |
| 21 | + | + | + | ++++ | +++ | + | + | + | + | + | + | + | + |
| 28 | + | + | + | ++++ | +++ | + | + | + | + | + | + | + | + |
| 31 | + | + | + | ++++ | +++ | + | + | + | + | + | + | + | + |
| 35 | + | + | + | ++++ | +++ | + | + | + | + | + | + | + | + |

* All patients in this table had genital mucous membrane lesions.

keratotic lesions or ulcers, measuring 5 to 10 mm. in diameter, on the shaft of the penis. He also had mucous membrane lesions of the glans penis and the oral cavity.

The skin manifestations are usually most prominent in those patients with severe arthritis. They are self-limiting, lasting from two to four

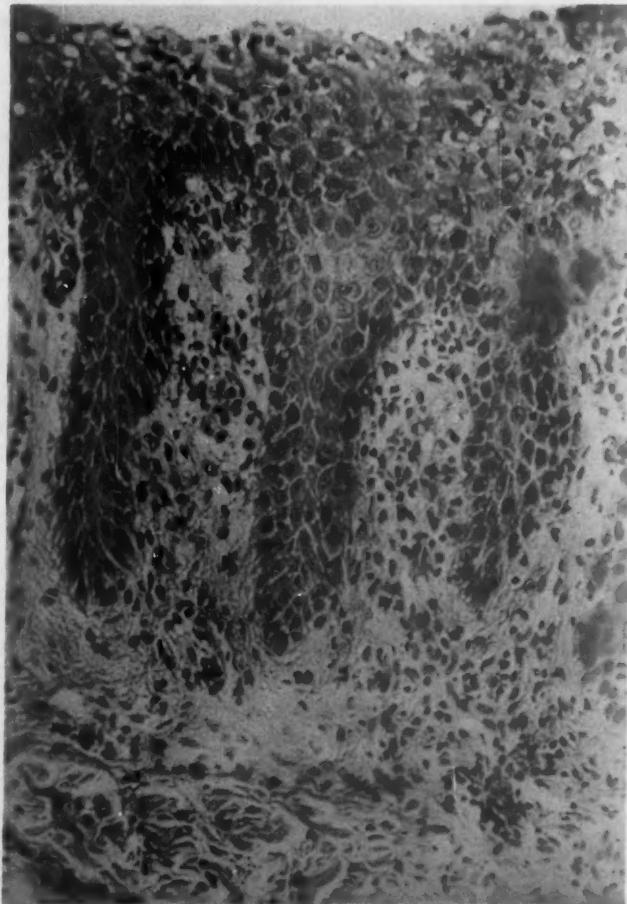


FIG. 6. Microscopic section of cutaneous lesion of Reiter's syndrome, showing elongation of the papillae with cellular infiltration about the rete pegs and edema of the connective tissue.

months, but may recur. The skin of all our patients healed and the nails grew out normally. The course was not influenced by penicillin or other antibiotics. Adrenocorticotropin and corticosteroids did not promote or prevent healing of the lesions.

Skin manifestations either are more frequent or at least have been reported more frequently in the endemic or venereal type of the syndrome. They may have been overlooked in the large series of the epidemic or dysenteric type. The slightly elevated, plaque-like lesions on the glans penis probably represent a variant of the hard, hyperkeratotic lesion, and are more often seen in the circumcised. The diffuse mucous membrane involvement of the foreskin and glans and the perimeatal lesions represent the soft parakeratotic type of lesion.

Histologically, keratotic lesions of Reiter's syndrome cannot be differentiated from pustular psoriasis, and are identical with so-called keratoderma blennorrhagica. As shown in figure 6, the rete pegs are elongated, and there is an increased number of lymphocytes and polymorphonuclear leukocytes with occasional eosinophils in the papillary tissues about them (figure 6). The superficial layers which in this section have been lost by desquamation often contain polymorphonuclear leukocytes. Edema of the deeper reticular layer of the skin is evident. Areas of hemorrhage may sometimes displace the basal cell layer.

The lesions of keratosis of Reiter's syndrome and those of keratoderma blennorrhagica are identical. It is our opinion that the latter term, which implies a gonococcal etiology, is a misnomer. The gonococcus is not responsible for these lesions.^{5, 6} The much higher incidence in Reiter's syndrome as compared with that in gonococcal infections is evidence that coincidental infection is the explanation in those patients with gonorrhea who present keratosis. Failure of antibiotic therapy to modify the course of the keratotic lesions is additional evidence.^{5, 6}

CONCLUSIONS

The high incidence of mucous membrane lesions in patients with Reiter's syndrome (80% in our series of 38 patients) is not generally appreciated. About half of the patients with painless genital lesions also have characteristic painless oral mucosal lesions. The keratosis of Reiter's syndrome, present in 11 of 38 patients (an incidence of about 30%), is, we believe, identical with what has been called keratoderma blennorrhagica. These lesions are uninfluenced by antibiotics or corticosteroids.

It is our opinion that mucocutaneous lesions may be as important in establishing the diagnosis of Reiter's syndrome as is nonspecific urethritis or conjunctivitis. In equivocal cases, when urethritis and/or conjunctivitis has not been observed or well documented, or in the incomplete form of the syndrome, the mucocutaneous lesions, known to appear from four to six weeks after the onset, may be diagnostic. In the endemic form, the triad of Reiter's syndrome might better be considered a tetrad, consisting in its complete form of urethritis, conjunctivitis, arthritis and mucocutaneous lesions.

SUMMARIO IN INTERLINGUA

Le incidentia de lesiones mucocutanee in pacientes con le syndrome de Reiter tractate in le curso de un periodo de 10 annos al Hospital Hines del Administration de Veteranos se monstrava plus alte que illo reportate in altere series. Trenta del 38 pacientes presentava erosiones perimeatal e/o lesiones de balanitis circinate, un incidentia de 80%. Vinti-tres habeva ambe lesiones. Quatro del remanente septe habeva erosiones perimeatal e tres balanitis circinate sol.

In plus, 14 de iste 30 pacientes (37% del gruppo total de 38) habeva indolor lesiones de membrana mucose oral, pharyngee, o glossal. Un numero del alteres habeva diffuse injectiones de palato e pharynge e plus obscur areas mucosal que representava possibilmente le stadio terminal de previe lesiones. Iste ultime casos non esseva considerate como characteristic e non esseva includite in le statistica.

Le ceratosis del syndrome de Reiter occurreva in 11 del 30 pacientes con lesiones mucosal (30% del gruppo total de 38 pacientes). Novem presentava dur e nodular lesiones hyperceratotic. Duo habeva molle areas paraceratotic. Nos crede que iste lesiones es identic con illos previamente designate como ceratosis blennorrhagie. Illos non es influentiate per antibioticos o corticosteroides.

In nostre opinion, lesiones mucocutanee es tanto importante pro le estableimento del diagnose de syndrome de Reiter como nonspecific urethritis o conjunctivitis. In casos equivoc, quando urethritis e/o conjunctivitis ha non essite observate o non es ben documentate, le lesiones mucocutanee, que se manifesta cognoscitemente inter quatro e sex septimanas post le declaration del condition, pote esser diagnostic. In su forma endemic, il es probabilmente preferibile designar le triade del syndrome de Reiter como un tetrade, consistente in su forma complete de urethritis, conjunctivitis, arthritis, e lesiones mucocutanee.

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MEDICAL EDUCATION

DEPARTMENTS OF MEDICINE IN 1970.

II. TEACHING POLICIES*

By ROBERT H. WILLIAMS, M.D., F.A.C.P., Seattle, Washington

A questionnaire was submitted to the head of the department of medicine at each medical school in the United States. A similar questionnaire was sent to full-time staff members of departments of medicine between the ages of 38 and 50 who were members of the American Society for Clinical Investigation and/or the Association of American Physicians. In a previous paper¹ certain premises and other background factors bearing upon the questions are reported, and opinions relative to many staff policies are presented. This paper deals with teaching policies.

PRE-COLLEGE EDUCATION

With the increase in necessary training following medical school graduation, and the increase in economic stress, it is desirable to reexamine all phases of the training program, especially from the point of view of possibly shortening some of the earlier school schedule and at the same time better preparing the physician not only for his medical school work but also for his entire career. The next three questions deal with the length of premedical training.

Do you favor shortening the pre-college training?

| | Yes | No |
|----------|-----|----|
| Chm. | 23 | 37 |
| Non-Chm. | 32 | 36 |

Do you favor shortening the average period for college premedical training and including some of the deleted material in the medical school curriculum?

| | Yes | No |
|----------|-----|----|
| Chm. | 21 | 35 |
| Non-Chm. | 27 | 37 |

Do you favor for college premedical training in most instances a period of:

| | Two Years | Three Years | Four Years |
|----------|-----------|-------------|------------|
| Chm. | 7 | 24 | 27 |
| Non-Chm. | 7 | 34 | 29 |

* Received for publication May 12, 1958.

From the Symposium on Whither Internal Medicine, presented in summary at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, May 1, 1958.

From the Department of Medicine, University of Washington School of Medicine, Seattle, Washington.

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Although the majority of the respondents did not favor shortening the pre-college training, a relatively large number did. Certainly this period is not used optimally at present. Only the minority favored shortening of the college training and inclusion in medical schools of some of the deleted material. As is shown in table 1, most of the replies indicated that three or four years of premedical training should be offered; a very small number favored only two years.

TABLE 1
Years Favored for Premedical Training

| Years..... | Two | Three | Four |
|------------|-----|-------|------|
| Chm. | 7 | 24 | 27 |
| Non-Chm. | 2 | 34 | 29 |

In recent years there has been a tendency among certain medical educators to de-emphasize the importance of physics, chemistry, biology and mathematics, but in the last year their importance has been re-emphasized. In reference to this subject the following question was asked:

Indicate the number of semester hours or years of training that you recommend in college:

Mathematics

Physics

Chemistry

Biology

As is seen in table 2, most of the replies favored from one to two years of biology, physics and mathematics, and from two to three years of chemistry.

TABLE 2
Amount of Certain Sciences Recommended in College

| Years..... | One | Two | Three | Four | Number of Votes |
|-------------|-----|-----|-------|------|-----------------|
| | | | | | |
| Mathematics | 20 | 27 | 2 | 2 | |
| Physics | 25 | 15 | 2 | 0 | |
| Chemistry | 5 | 20 | 19 | 1 | |
| Biology | 22 | 20 | 2 | 0 | |

MEDICAL SCHOOL EDUCATION

Number of Students per Class: The number of medical students per class in most schools ranges from approximately 50 to 200. However, the number in some schools is more than is desired by the respondents to the following question:

How many students per class do you consider optimal?

One respondent desired fewer than 50, and four (in both groups combined) wanted more than 100 students. The preference of all the other respondents ranged from 50 to 100 (table 3), with 75 as the mode.

TABLE 3
Number of Students per Class Considered Optimal

| No. Students | 50 | 60 | 70 | 75 | 80 | 85 | 90 | 100 |
|--------------|-----------------|----|----|----|----|----|----|-----|
| | Number of Votes | | | | | | | |
| Chm. | 9 | 6 | 7 | 17 | 6 | 0 | 3 | 9 |
| Non-Chm. | 3 | 10 | 6 | 15 | 7 | 3 | 1 | 17 |

Financing of Student Education:

Assuming that it costs approximately \$2,500 per year per student, what percentage of this should be paid by:

- (a) The medical student while in school?
- (b) The medical student while in school, plus later?
- (c) The Federal or State Government?
- (d) Scholarships?

Since the summation of the percentages selected by some respondents exceeded 100, table 4 was composed not to show percentages, but to indicate that most persons desired that part of the students' education be paid by the student, part by the Government, and part by scholarships. Very few thought that all of the cost of education should be paid from any one of the sources mentioned. The majority of the respondents indicated that the medical student should pay for from 20 to 60% of his total educational cost, either while in school or later; a few thought he should pay the total cost, and a few thought he should pay none. Most of the replies suggested that the Federal or State Government should pay for from 20 to 50% of the cost, and that from 10 to 30% should be paid from scholarships. It is evident that there is a rapidly increasing desire for the Government to pay for all or a major part of the education. Under

TABLE 4
Payment for Medical Students' Education

| | None | Part | All |
|--|-----------------|------|-----|
| | | | |
| | Number of Votes | | |
| By medical student while in school | | | |
| Chm. | 2 | 43 | 0 |
| Non-Chm. | 3 | 53 | 0 |
| By medical student while in school, plus later | | | |
| Chm. | 9 | 27 | 5 |
| Non-Chm. | 5 | 38 | 2 |
| By federal or state government | | | |
| Chm. | 6 | 36 | 3 |
| Non-Chm. | 2 | 47 | 1 |
| By scholarships | | | |
| Chm. | 3 | 35 | 1 |
| Non-Chm. | 0 | 40 | 3 |

the present circumstances it would be very helpful for the student to be able to procure loans easily at little or no interest.

Integrated Teaching:

Do you believe that most departments of medicine should do considerably more teaching of students during the first one and one-half years?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 25 | 36 |
| Non-Chm. | 33 | 37 |

Should basic scientists do considerably more teaching in the fourth year?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 42 | 19 |
| Non-Chm. | 49 | 21 |

Should all staff members engaged in the same specialty, irrespective of departmental affiliation, have conferences for the organization of the teaching in the respective fields throughout the four years?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 56 | 5 |
| Non-Chm. | 64 | 8 |

Should each be familiar with the broad plans of the others?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 58 | 3 |
| Non-Chm. | 71 | 1 |

Should there be a marked increase in conjoint conferences, with crossing of interdepartmental and interdivisional lines?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 47 | 15 |
| Non-Chm. | 51 | 20 |

It is my impression that most medical schools should increase tremendously the amount of vertical teaching. This type is apparently more efficient, interesting and valuable to the student. Whereas it may require more faculty time, in proportion to true education of the student it might require less time. Of course, compared with horizontal, vertical teaching necessitates more teaching by clinical scientists in the first years, and by basic scientists in the last years, more conjoint exercises, better acquaintance with the teaching of others, and more interdepartmental coöperation. At present there are too much repetition and too many omissions, and too little organization and coördination.

Time for Research, Electives and Other Activities:

How many months of solid elective time do you favor in:

1st year , 2nd year , 3rd year , 4th year ?

A progressive increment of block time for electives was desired throughout the four years (table 5). The majority preferred no block time in the first

year, from one to two months in the second, one to three months in the third, and two to four months in the fourth.

It certainly seems worth while to provide sufficient elective time, particularly with the increase in specialization. This permits the student to broaden his training and to increase in depth in certain areas. During this time many students derive significant benefit from research. These various activities often exert a marked influence upon the student's entire career.

Do you favor 11 months of school (including an elective quarter) for each student during:

| | 2nd Year | 3rd Year | 4th Year |
|----------|----------|----------|----------|
| Chm. | 28 | 42 | 53 |
| Non-Chm. | 31 | 53 | 56 |

A large majority considered it desirable to offer 11 months of school for the third and fourth years. Moreover, a significant number wanted a similar

TABLE 5
Solid Elective Time for Students

| Months..... | 0 | 1 | 2 | 3 | 4 | 5+ |
|-------------|-----------------|----|----|----|----|----|
| | Number of Votes | | | | | |
| First Year | | | | | | |
| Chm. | 24 | 10 | 5 | 4 | 0 | 0 |
| Non-Chm. | 36 | 13 | 9 | 4 | 0 | 0 |
| Second Year | | | | | | |
| Chm. | 10 | 11 | 17 | 11 | 0 | 0 |
| Non-Chm. | 21 | 15 | 18 | 7 | 1 | 0 |
| Third Year | | | | | | |
| Chm. | 3 | 16 | 11 | 21 | 3 | 1 |
| Non-Chm. | 5 | 10 | 26 | 23 | 0 | 0 |
| Fourth Year | | | | | | |
| Chm. | 0 | 8 | 11 | 25 | 10 | 3 |
| Non-Chm. | 0 | 7 | 13 | 29 | 12 | 6 |

pattern for the second year. The students need to spend this amount of time to cover the appropriate amount of material. This makes it easier to offer electives, including research. Research experience has frequently proved valuable, even for those who know they want to engage in full-time practice. In this connection, I was interested in the statement of a general practitioner in a small town: "My son is in your fourth year class and after he has internship and residency training he is to go to the Far East as a medical missionary. Since he will be faced with many interesting and difficult medical problems, and since there will be no other doctors nearby, I hope you will convince him to spend a year in research so that he can work out these problems more satisfactorily." When the son was confronted with this suggestion he stated: "Since spending last summer in research I need no convincing—I think every student should spend some time in research, even if he knows he wants to engage in general practice."

Some of the students with sufficient interest and capability in research should be encouraged to withdraw from medical school for a year to participate exclusively in research. Most of the respondents expressed a similar view. Not only does this experience often exert a great influence upon the career of the student, but the specific project has also occasionally resulted in a great contribution.

Do you favor encouraging selected students with research promise to drop out of school for a year in order that they may engage in research?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 47 | 13 |
| Non-Chm. | 47 | 25 |

Relative Time Devoted to Medicine:

Do you believe more time should be devoted to Medicine?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 33 | 27 |
| Non-Chm. | 31 | 38 |

I do not know how well the vote upon this subject correlates with present time allocations to Medicine in different medical schools. Certainly there are significant differences. To provide more time for Medicine, reduction in time for several other departments was recommended. Surgery and its specialties were suggested most frequently, followed by psychiatry and obstetrics-gynecology, which were listed with equal frequency.

To obtain a clearer opinion of the relative amount of time that should be devoted to clinical subjects, the following question was asked:

What percentage of the student's third and fourth years combined, excluding elective time, should be allocated to the following departments:

| | | | | | |
|------------|-----|---------------|-----|-----------|-----|
| Medicine | 33% | Psychiatry | 11% | Radiology | 6% |
| Ob. & Gyn. | 11% | Prev. Med. & | | Surgery | 23% |
| Pediatrics | 14% | Public Health | 6% | | |

The average percentage of time recommended for allocation to some of the departments is doubtless less than that possessed by them at present. The proposed reduction is probably based on a visualization of a great growth of the specialties, and the lack of necessity for everyone to try to learn all of these skills, since many physicians will not engage in some of the specialties. Moreover, it is easier to teach certain specialties to house officers than to students. With this as one factor in mind, it was proposed that the fourth year be changed to a rotating internship, but, as indicated later, most respondents disapproved of this plan.

Recently there has been considerable discussion in some schools relative to increasing significantly the amount of Medicine taught in the third year, and reducing that in the fourth year. However, the answers to the following question indicate that most respondents did not approve of such a plan:

Do you favor giving significantly more Medicine in the third year, with some reduction in the fourth?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 14 | 44 |
| Non-Chm. | 20 | 50 |

The replies to the following question show that the majority do not wish to transfer a significant quota of medical instruction from the fourth year to earlier years, though this would be necessary in order for the fourth year students to perform well as rotating interns.

Do you favor having students spend the fourth year in the capacity of rotating interns?

| <i>Yes</i> | <i>No</i> |
|------------|-----------|
| 22 | 49 |

Place in Curriculum for Preventive Medicine, Practice Apprenticeship, Sociologists and Psychologists: As indicated in the next question, the vast majority of replies favored interdigitating the teaching of preventive medicine conjointly with that of other departments. This certainly seems to me to be the most interesting, clearest and most efficient way to present the material.

Should preventive medicine teaching:

(a) Be interdigitated in a conjoint manner with that of the other departments?

| | <i>Yes</i> |
|----------|------------|
| Chm. | 52 |
| Non-Chm. | 56 |

(b) Be given in separate courses?

| | |
|----------|----|
| Chm. | 10 |
| Non-Chm. | 15 |

In recent years, sociologists and psychologists have played an increasingly important role in teaching medical students and in patient care. However, as is brought out by the next question, a large proportion of the respondents do not favor an increase.

There is a strong demand by some individuals for a far greater role to be played in medical education and patient care by: (a) psychologists, and (b) sociologists. Do you favor this increase?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 15 | 43 |
| Non-Chm. | 12 | 57 |

There also has been much more emphasis upon having students follow patients at home, but as is shown by the answer to the next question, a great majority of those replying favored no type of "home care" program.

Do you favor any type of "home care" program?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 20 | 39 |
| Non-Chm. | 17 | 53 |

Likewise, a large proportion of the replies indicated a disapproval of having students work full-time with a physician in practice.

Do you favor having students work full-time with a physician in practice?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 10 | 51 |
| Non-Chm. | 10 | 59 |

Faculty Advisors for Students: With the increase in the size of medical schools, the great increase in specialty training and the resultant decrease in association with any one staff member, and the earlier marriage of students with consequent domestic complexities, many more students than in the past need help and advice from one or more members of the faculty. This view is approved by the answers to the following questions:

Do you believe that the full-time staff should spend considerably more time discussing with students their future objectives, both in groups and with individual students?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 46 | 13 |
| Non-Chm. | 48 | 22 |

Do you believe each medical student should be assigned a faculty member as a tutor, or be encouraged to select one?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 39 | 19 |
| Non-Chm. | 50 | 21 |

INTERNS AND RESIDENTS

Training:

For one who is convinced that he wants to specialize in Internal Medicine, do you favor a straight internship over a rotating internship?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 39 | 21 |
| Non-Chm. | 59 | 13 |

The question of the relative merits of a rotating internship versus a straight internship is hotly debated. The foregoing question, however, is specifically restricted to the "one who is convinced that he wants to specialize in Internal Medicine." With this in mind, the great majority of respondents favored a straight internship. Whereas in a rotating internship greater knowledge is acquired in subjects other than medicine, less is learned at the time about internal medicine, so this must be obtained later, thus increasing the period of training.

How many years of training "in the white suit" should be received by one who is going to engage in general practice?

As is shown in figure 1, almost all of the respondents thought that a physician planning to engage in general practice should spend two or three years "in the

**YEARS OF INTERNSHIP AND RESIDENCY
FOR GENERAL PRACTICE**

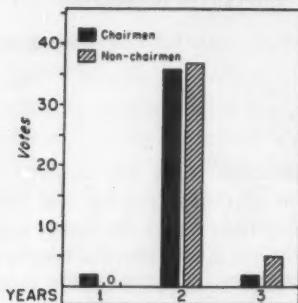


FIG. 1.

"white suit" (internship and residency). Although only two thought that one year was sufficient, nine felt that four or more years were needed.

What do you consider to be the optimal number of years of resident training in general internal medicine for one who wants to engage in:

- The practice of general internal medicine?
- The practice of a special phase of internal medicine?
- An academic career in a special phase of internal medicine?

The answers to these questions are presented in figure 2. The mode of three years for one who plans to engage in general internal medicine conforms to my own opinion. However, for one who plans to deal almost entirely with a special phase of internal medicine, whether in practice or in an academic

OPTIMAL NUMBER OF YEARS FOR RESIDENCY TRAINING

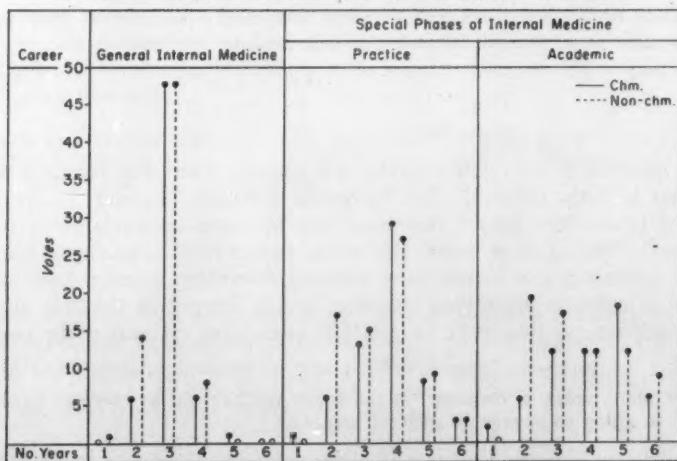


FIG. 2.

career, I believe that two years of residency training are usually sufficient, but it is desirable for him to have not less than two years. Even the student who desires to limit his activities to one field needs to have a fairly good knowledge of Medicine. This is necessary in differential diagnosis and in dealing with the many disorders that occur coincidentally with the one in his specialty. In addition to this broad training, he should have two or three years of training in his specialty.

How many years of residency training (internship not included) should ordinarily be obtained in general internal medicine before the specialty training is started?

The majority of the respondents favored two or three years of residency training in general internal medicine before the specialty training is started (figure 3).

Training in most of the specialties of Medicine is via traineeships or research fellowships. Do you favor an increase in the number of specialty residencies offered?

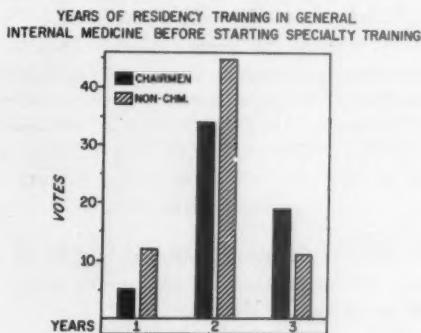


FIG. 3.

It is evident in table 6 that an increase in the number of specialty residencies is desired. These are helpful to the teaching program for the specialty resident, the students and house officers. However, the training offered under the category of research fellowships is also very important, particularly for one engaging in academic medicine.

Do you believe that the general patterns for training in the various specialties of Medicine should be fairly similar?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 42 | 16 |
| Non-Chm. | 55 | 14 |

I concur with the majority vote that it is desirable for each of the specialists in Medicine to have two years of residency in general internal medicine, and then two or three years of training in his respective specialty.

Do the present requirements for certification by the Board of Internal Medicine conform fairly well to your own opinion?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 51 | 9 |
| Non-Chm. | 52 | 18 |

Do you believe that much too much pressure has been exerted for special privileges by the:

| | <i>Yes</i> | <i>No</i> |
|-----------------------|------------|-----------|
| (1) Neurology Board | 20 | 20 |
| (2) Dermatology Board | 20 | 20 |

Whereas most of the respondents approve of the present requirements for certification by the Board of Internal Medicine, a significant number believe that too much pressure for special privileges has been exerted by the Neurology Board and the Dermatology Board. On the basis of certain comments made by the respondents and others, as well as my own experience, I wish to propose that all of the specialties in Medicine be handled similarly. An examination in general internal medicine should be given, and then an examination in the

TABLE 6
Amount of Increase in Residencies in Specialties in Medicine Favored

| | None | Slight | Moderate | Marked |
|----------|------|--------|----------|--------|
| Chm. | 19 | 13 | 23 | 5 |
| Non-Chm. | 12 | 19 | 34 | 6 |

specialty. Administration of the examination should be by a subspecialty board composed of members within and outside of a given specialty, operating under policies for all of the specialties in Medicine.

Do you favor a matching plan for residents comparable to that for interns?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 7 | 54 |
| Non-Chm. | 7 | 61 |

Whereas the present system relative to the appointment of residents has unsatisfactory features, particularly since they are made so long in advance, very few individuals favored a matching plan comparable to that for interns.

Income, License and Insurance:

Bearing in mind the assumption that essentially all patients will become paying patients, and that the present economic status prevails, what do you consider to be the appropriate annual pay for the following (assuming that the house officer must pay for room, board, laundry, hospitalization, etc.)?

| | |
|-------------------|---------|
| Interns | \$..... |
| 1st year resident | \$..... |
| 2nd year resident | \$..... |
| 3rd year resident | \$..... |

ANNUAL SALARY FOR INTERNS AND RESIDENTS

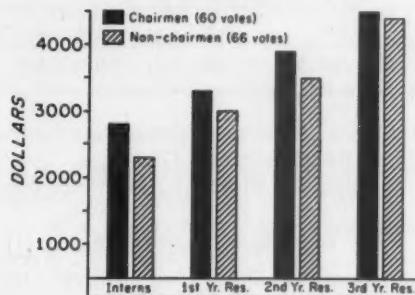


FIG. 4.

The average recommended salaries shown in figure 4 are distinctly larger than at present. However, the salaries at present are distinctly low, particularly for the upper level of residents, who contribute markedly to excellent care of the patients. In view of this fact, and the increase in the number of paying patients being used in teaching centers, the question arises as to whether a senior resident might be permitted to submit a bill for professional service when he has taken chief care of the patient. Such a plan seems to me to face the problem realistically, but it is not endorsed by a large majority of the respondents. When a resident is permitted to submit bills, his total income should not be proportionate to his income from professional fees.

Do you favor urging residents to obtain the following, assuming that they receive appropriate salaries?

- License
- Malpractice insurance
- Blue Cross (or equivalent)
- Blue Shield (or equivalent)

As shown in table 7, the majority of the respondents recommended that residents obtain a license to practice and purchase malpractice insurance; this is particularly indicated with the increasing number of malpractice suits. It is also helpful for them to have insurance for hospitalization and professional care

TABLE 7
License and Insurance for Residents

| | Chm. | | Non-Chm. | |
|-----------------------------|------|----|----------|----|
| | Yes | No | Yes | No |
| License | 56 | 4 | 62 | 8 |
| Malpractice insurance | 46 | 13 | 52 | 14 |
| Blue Cross (or equivalent) | 59 | 2 | 63 | 7 |
| Blue Shield (or equivalent) | 34 | 21 | 34 | 30 |

TABLE 8
Number of Research Fellows Now in Each Department of Medicine

| No. Research Fellows..... | 0-5 | 6-10 | 11-15 | 16-20 | 20+ |
|---------------------------|-----|------|-------|-------|-----|
| No. Depts. of Med. | 23 | 14 | 9 | 4 | 5 |

for themselves and family. This assures them proper attention, and is better for both the hospital and the physicians. Of course, these extra expenditures should be taken into consideration when the salaries are being formulated.

RESEARCH FELLOWSHIP

Present Number of Research Fellows: How many research fellows or trainees are in the department of medicine? The majority of departments do not have more than ten research fellows, but a few have more than 20 (table 8). This number will probably increase significantly with the many fellowship grants now available, the decrease in the military needs, and the increased necessity for this training.

Training Programs: At present, most of the physicians who are trained as specialists in one phase of internal medicine obtain the training as a Research Fellow or Trainee. Many of these enter practice, but a few enter academic medicine. The questions below pertain only to those with good possibilities of entering academic medicine.

Do you favor offering the research fellowship training before or after completion of the "white suit" training?

| | Before | After |
|----------|--------|-------|
| Chm. | 4 | 48 |
| Non-Chm. | 3 | 60 |

If research fellowship training is taken before the completion of the "white suit training," there is an earlier, intense stimulation of interest in research. Moreover, having physicians with research background on the resident staff is

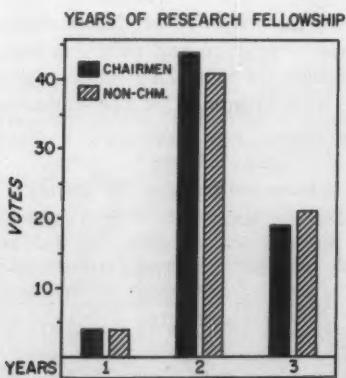


FIG. 5.

stimulating to the students, house officers and others. It has, however, the great disadvantage of interrupting the research program of the individual. Moreover, some of the group become so intensely interested in their research that they do not complete their residency training. Consequently, my reaction is in accord with the great majority of the respondents, who recommend that the research fellowship training follow completion of the residency training.

How many years of research fellowship should the average person obtain?

It is desirable for most of the physicians who plan to engage in academic medicine to obtain research fellowship training for two or three years (figure 5). Of course, as indicated by some of the respondents, it may be desirable in certain instances to extend this to four years or more.

Should there be a considerable increase in:

- The systematic training offered this group in basic science courses?
- General principles of research?
- Detailed instruction in experimental design?
- Laboratory technics?
- Biometrics?
- Detailed instruction in paper writing?
- Detailed instruction in the presentation of papers?

Research has become distinctly more professional and complicated in recent years. It is therefore advisable to offer considerably more training in it than in the past. Experience has demonstrated that most Research Fellows need additional training in philosophies and objectives of research, in biometrics, experimental design, the writing and presentation of papers, instrumentation, laboratory regimens, and animal characteristics. Some may need additional course training in chemistry, physics, mathematics or other basic sciences. My own experience in several medical centers has demonstrated that much of this is neglected, but this is less likely to occur if it is systematically planned and some of the best talent is utilized.

Unquestionably, the research fellow will obtain the most information through experience in research while working closely with one who is skilled in investigation. However, where there is a fairly large number of research fellows in a Department, and there are experts in various principles of research, it is advantageous to present some of the material systematically to the group. The entire group need not engage in all phases of the training program, because there are differences in previous individual training and future plans.

Staff members from other departments, particularly the basic sciences, can be of great assistance. However, of even greater aid are the basic science staff members of clinical departments. They help to teach not only the general principles of research, but also the detailed procedures. Moreover, they are more available in the laboratory than are most clinicians.

Financial Remuneration:

With maintenance of the present economic structure, how much money should the average research fellow be paid, assuming he has had three years in the "white suit," and assuming that he is married and has one child?

1st year , 2nd year , 3rd year

The amount of pay for research fellows shown in figure 6 conforms fairly well to my own opinion. At present, I do not believe we make enough differentiation between levels of merit and the quality and quantity of contributions. The pay for the second year of research fellowship should be much better than that for the first, and that for the third year should be considerably better than that for the second. There should also be some differentiation in the amount of residency training, particularly in the range from none to three years. It is important for the research fellow to engage solely in his research, except for a little teaching, so he should be paid appropriately, and not be permitted to get involved in "side jobs."

POSTGRADUATE TRAINING

The need for postgraduate training is increasing rapidly because of the tremendous progress in medicine. Whereas the practicing physician acquires

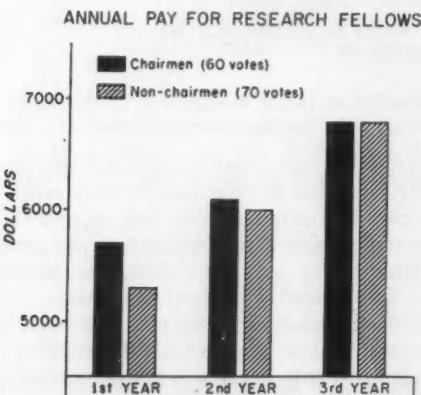


FIG. 6.

much of his new knowledge through journals, books, and meetings of medical societies, education via postgraduate courses is increasing significantly. A common problem is to select and present the material in the appropriate manner for the registrants, since they often differ markedly in knowledge, ability and interest. The courses given by specialists should be designated accordingly. There is less duplication in the longer courses than in the shorter ones. To utilize the instructors' and registrants' time most effectively, it seems worth while to present some serial courses designed systematically for certain groups. This opinion was supported by the majority of answers to this question:

Do you favor an attempt at giving, over a period of years, well organized serial courses designed systematically for some specific groups?

| | Yes | No |
|----------|-----|----|
| Chm. | 49 | 11 |
| Non-Chm. | 49 | 20 |

I favor giving some examinations occasionally as an aid in designing courses of appropriate types, duration and frequency. Whereas many of the respondents favor this plan, the majority do not.

Do you favor giving some examinations as an aid in designing the most appropriate types, duration and frequency of courses?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 26 | 32 |
| Non-Chm. | 25 | 40 |

However, the majority do favor requiring a certain amount of postgraduate training periodically, as brought out by the following question:

Should a certain amount of postgraduate training be required periodically?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 40 | 21 |
| Non-Chm. | 39 | 29 |

It is nice to think that all practicing physicians will keep abreast of medical progress in their respective fields, but many do not and, indeed, some are pitifully negligent in this regard. It is desired that, by working through medical societies and other agencies, all physicians will work out plans for themselves for the appropriate amount of continuous education. The majority of the questionees did not favor giving periodic examinations to practicing physicians.

Should periodic examinations (e.g., at intervals of 10 years) be given to practicing physicians?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 23 | 34 |
| Non-Chm. | 26 | 41 |

Opinion was evenly divided with respect to whether registration fees for postgraduate courses should support all such activities. There are significant advantages and disadvantages in such a plan.

Do you believe that registration fees from postgraduate courses should support all such activities?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 32 | 25 |
| Non-Chm. | 30 | 37 |

Since the type of training and type of practice are interrelated, the following question was asked:

Do you think that considerable encouragement should be given to physicians in:

- (a) Becoming a member of an organized group of 10 or more physicians geographically adjacent, but financially independent?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 36 | 10 |
| Non-Chm. | 46 | 14 |

(b) Becoming a member of a large clinic with financial interdependence?

| | <i>Yes</i> | <i>No</i> |
|----------|------------|-----------|
| Chm. | 33 | 14 |
| Non-Chm. | 42 | 19 |

(c) Should (a) or (b) increase more?

| | <i>(a)</i> | <i>(b)</i> |
|----------|------------|------------|
| Chm. | 19 | 21 |
| Non-Chm. | 26 | 25 |

It is not surprising that the majority believe that there should be a significant increase in group practice, of the type with financial interdependence or financial independence. This is indicated particularly with the great increase in the number of specialists required and the desire for good teamwork between them. Moreover, there is a need for convenient and common usage of laboratory facilities and expensive equipment. These clinic plans permit more systematic planning for additional education and research, as well as home and other activities. Since such plans should be more efficient, they may lead to more extensive and less expensive care of the patient.

SUMMARY AND CONCLUSIONS

This paper presents data derived from replies to a questionnaire submitted to the head of the Department of Medicine in each medical school in the United States, and to more than 100 other full-time staff members in medicine. The following opinions were indicated by a distinct majority of the respondents:

Three or four years of premedical training were favored, including one to two years of biology, physics and mathematics, and two to three years of chemistry.

From 50 to 100 medical students per class, with a mode of 75, were considered to be optimal.

All staff members engaged in the same specialty, irrespective of departmental affiliation, should have conferences for the organization of the teaching in the respective fields throughout the four years; each should be familiar with the broad plans of the others. There should be a marked increase in conjoint conferences, with crossing of interdepartmental and interdivisional lines.

No block time for electives was favored for the first year; one to two months were favored in the second, one to three months in the third, and two to four months in the fourth. It was considered desirable to offer 11 months of school for the third and fourth years. Selected students with research promise should be encouraged to drop out of school for a year in order that they may engage in research.

The following average percentages of the time during the students' third and fourth years combined, excluding elective time, were favored: medicine, 33; surgery, 23; pediatrics, 14; obstetrics-gynecology, 11; psychiatry, 11; preventive medicine and public health, 6; radiology, 6. There was disapproval of having students spend the fourth year in the capacity of rotating interns. Interdigitating teaching in Preventive Medicine in a conjoint manner with that of the other Departments was preferred to giving it in separate courses. There

was disapproval of sociologists and psychologists playing a far greater role in medical education and patient care. No type of "home care" program was favored. Having students work full-time with a physician in practice was not desired. It was believed that the full-time staff should spend considerably more time discussing with students their future objectives and that each medical student should be assigned a faculty advisor.

For one who is convinced that he wants to specialize in Internal Medicine, a straight internship was preferred to a rotating internship.

A physician who is planning to engage in general practice should spend two or three years in house officer training. The optimal number of years of residency training in general Internal Medicine for one who wants to engage in the practice of Internal Medicine is three; ordinarily, two or three years are desired before specialty training is started. An increase is desirable in the number of specialty residencies offered. The general pattern for training in the specialties of medicine should be fairly similar.

The present requirements for certification by the Board of Internal Medicine seem satisfactory. A matching plan for residents comparable to that for interns is not desired. Residents should be encouraged to obtain a license to practice medicine, to purchase malpractice insurance, and to purchase insurance for hospitalization and medical care.

It is preferable for all of the house officer experience to be completed before beginning research fellowships. The fellowship training in most instances should last for two or three years. More systematic instruction in some of the broader aspects of research should be offered.

Research Fellows, and particularly residents, should have an increase in financial remuneration.

It is desirable to attempt giving, over a period of years, well organized serial postgraduate courses designed systematically for some specific groups; a certain amount of postgraduate training should be required periodically.

Considerable encouragement should be given to many physicians engaging in practice to become members of an organized group of 10 or more physicians geographically adjacent, but financially independent, or to become members of a large clinic with financial interdependence.

ACKNOWLEDGMENTS

I am glad to indicate my deep appreciation to the many staff members who gave so freely of their time in responding to a questionnaire that I submitted to them. This material serves as the major basis for this paper.

The great assistance of Mrs. Marguerite Brown and Mrs. Priscilla Crittenden is also acknowledged.

SUMMARIO IN INTERLINGUA

Iste articulo presenta datos que esseva colligite per medio de un questionario submittite al chefes de departamento de medicina in omne le scholas de medicina del Statos Unite e a plus que 100 membros regular de varie facultates de medicina. Le sequente opiones esseva exprimite per distincte majoritates del respondentes.

Tres a quattro annos de instruction premedical esseva recommendate, incluse un a duo annos de biologia, de physica, e de mathematica e duo a tres annos de chimia.

Classes de inter 50 e 100 studentes medical—generalmente 75—esseva considerate como optimal.

Omne le membros del facultate concernite con le mesme specialitate, sin reguardo a lor affiliation departmental, deberea participar in conferentias pro le organisation del modos de instruction in le varie campos a omne nivello del curso de quatro annos. Omne membro individual del facultate deberea esser familiar con le planos general de su collegas. Deberea evenir un augmento marcate de conferentias juncte con participantes ab plure departimentos o plure divisiones.

Esseva recommendate pro studios facultative (1) nulle tempore durante le prime anno, (2) un a duo menses durante le secunde anno, (3) un a tres menses durante le tertie anno, e (4) duo a quattro menses durante le quarte anno. Esseva considerate como desirabile le provision de 11 menses de schola durante le tertie e le quarte anno. Seligite studentes qui es promittente in un campo de recerca deberea esser incoragiate a quitar le schola pro un anno de maniera que illes pote occupar se de labores specialisate in ille campo.

Pro le studente convincite de su desiro de specialisar se in le medicina interne, un sistema de internantia uniforme e non rotatori esseva preferite.

Un medico qui plana entrar in un practica general deberea passar duo a tres annos de servicio como medico de casa in un hospital general. Le numero optimal de annos de servicio como internante in le campo de medicina interne general es ordinariamente tres annos pro le individuo qui vole occupar se de practicar le medicina interne. Duo a tres annos es considerate como desirabile ante le comenciamiento de un trainamento specialisate. Un augmento es desirabile in le numero del postos de residentia in le varie specialitates. In general, le modo de trainamento in le specialitates de medicina deberea esser satis identic.

Il es preferibile que le servicio de medico de casa es completate ante le comenciamiento de ulle labores como fellow de recerca. Le trainamento de fellows de recerca deberea durar, in le majoritate del casos, inter duo e tres annos. Un instruction plus systematic in certes del aspectos general de recerca deberea esser offerite.

Medicos de practica general deberea esser incoragiate energicamente a facer se membros de un gruppo organise de 10 collegas o plus qui es geographicamente vicin le unes al alteres sed qui es financialmente independente o facer se membros de un grande clinica con interdependentia financial.

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CASE REPORTS

PHEOCHROMOCYTOMA: A CASE OF PAROXYSMAL HYPERTENSIVE ATTACKS INDUCED BY EATING AND CHANGE OF POSITION *

By HILLEL L. HORN, M.D., Rochester, N. Y.

A pheochromocytoma is a challenging tumor to recognize and one that can be most gratifying for the physician as he sees a clinical cure result from its removal. It is a chromaffin cell tumor, most often found arising from the adrenal medulla, but one that may develop wherever chromaffin tissue is found, as in the paraganglia of the sympathetic nervous system. There is no difference in sex distribution,¹ although a familial incidence has previously been noted.^{2, 3} The tumor is more commonly found in the right adrenal gland. Approximately 10% are bilateral; a similar percentage is malignant.¹

The clinical picture which such a tumor presents is the result of the secretion of abnormal amounts of epinephrine and norepinephrine into the bloodstream. However, because these substances are not present in a constant proportion from one tumor to another, the clinical results are quite variable.⁴ For this reason pheochromocytoma has been quite aptly called the "great mimic" in hypertensive disorders.⁵ The clinical pictures most often described are those relating to persistent hypertension, and the less frequent but more dramatic cases presenting with attacks of paroxysmal hypertension. Some cases are mistaken for essential hypertension⁴ and some for hyperthyroidism.⁶ A few are asymptomatic and found only at autopsy, or unexpectedly during the course of tests or procedures. In rare instances Addison's disease has resulted from destructive pressure of the tumors on the adrenal cortices.⁷

It is the purpose of this paper to present an unusual case of pheochromocytoma to document the rare occurrence of eating as a paroxysmal precipitating factor, and to corroborate the excellent results obtainable by presacral air insufflation in helping to localize the tumor preoperatively.⁸

CASE REPORT

History and Physical Examination: The patient, a 41 year old Negro male, was admitted to the hospital with a one-hour history of abdominal pain and the coughing up of pink sputum. While having a cold drink he had experienced the sudden onset of severe epigastric pain without any radiation, nausea or diaphoresis. Shortly thereafter he had begun to cough up pink sputum. He had some shortness of breath, became very frightened and walked into the emergency room.

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From the Medical Service of the Rochester General Hospital, Rochester, N. Y.

This paper was co-winner of the 1957 Monroe Pharmacy prize awarded by the Rochester Academy of Medicine.

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According to his old record (dating back four years), the patient had complained of a feeling of fullness, gas and vague pain in the epigastrum when he ate meat, especially pork. An initial blood pressure was 140/90 mm. of Hg. An upper gastrointestinal series showed a persistent deformity of the duodenum compatible with the diagnosis of duodenal ulcer. The patient was placed on a convalescent ulcer diet and an antacid, and became asymptomatic.

The patient was seen again on four separate occasions—from two and a half years until nine months before the present admission—for such complaints as "upper abdominal discomfort" and "gas and bloating," always after meals, incitants at those times having been listed as meat, fried or spicy foods, and soup. Each time his symptoms had cleared with diet and antispasmodics. Two months before the acute episode he had again complained of gas and bloating, which had persisted intermittently until admission. Upper gastrointestinal x-ray series were normal eight months and again one month before admission.

On the admission physical examination the patient had a temperature of 97.4° F. rectal; pulse, 80 to 100 per minute and regular; respiration, 44 per minute; blood pressure, 160/80 mm. of Hg. He appeared to be a well developed, well nourished male in acute respiratory distress but not diaphoretic. He was alert and very anxious, moving all over the bed and coughing up copious amounts of pink sputum. The thyroid was not felt. Bilateral bubbling râles were heard all over the chest. There was no rub. The heart sounds were difficult to evaluate because of the râles. Later examinations revealed a transient aortic systolic murmur on the eighth day, and a persistent grade 2 apical systolic murmur from the eleventh day on. The upper abdomen was diffusely tender, but mostly in the midline. There was muscle guarding but no rebound tenderness, and bowel sounds were active. The extremities were cold, without any edema.

Course in Hospital: The patient responded well to the therapy for acute pulmonary edema, despite the occurrence of arrhythmias and some marked electrocardiographic changes. He was lethargic and had residual epigastric soreness. Initial diagnostic impressions included pulmonary infarction, myocardial infarction and a perforated viscus. After the latter had been ruled out and additional information obtained, the patient was started on an anticoagulant. (He had had tiredness and aching in his right calf after work for five years, worse during the preceding six months.) This therapy was continued for three days. On the third and fourth days the prothrombin time was prolonged beyond the therapeutic level despite conservative initial doses; this returned to a normal level after vitamin K₁ administration and withdrawal of the anticoagulant.

During the first 48 hours the patient's blood pressure varied, usually between 160/80 and 180/100 mm. of Hg. On two occasions it was found to be 110/80 mm. of Hg, but when checked again it was found to be elevated. On the third hospital day the blood pressure was unexpectedly found to be 70/50 mm. of Hg. The patient was complaining almost constantly of epigastric pain, and a Levophed infusion was started. This was continued for a period of 14.5 hours. It was difficult to regulate his blood pressure, especially when he was turned on his side; it ranged anywhere from 70/56 to 220/120 mm. of Hg. At various times he was noted to be quite diaphoretic and to have cold extremities. There was a tachycardia with occasional extrasystoles. There was no pupil dilatation or "goose-flesh." The blood pressure continued to fluctuate after the Levophed was discontinued, now ranging from 70/50 to 250/140 mm. of Hg. The latter was found after a routine abdominal examination. A similar finding was obtained after intentional abdominal massage, but when blood pressure stabilization was awaited thereafter the patient reacted the same way spontaneously (figure 1). It was noted that he was awake and restless when the blood pressure was at hypotensive levels, and semicomatoscopic when it was elevated. These

attacks gradually ceased in the next 18 hours. With this information, a number of tests were performed to confirm the clinical impression of a pheochromocytoma and to determine its location. After many tests and the demonstration of a right suprarenal tumor (figure 2), the patient was prepared for surgery and an operation was performed on the twenty-eighth hospital day.

Before the operation many attempts were made to elicit a history of paroxysmal attacks. The patient claimed only to have had episodes of dizziness and sweating while doing his usual work as a janitor. On the seventeenth day he stated that for about one to one and a half years he had had some dizziness and sweating when at home or not particularly engaged in any hard work. These episodes would last for from one to three minutes, occasionally for five minutes, and he would stop whatever he was doing at the time. Such episodes would occur perhaps one to two times a month. The night before the operation, on further questioning, he stated for the first time that for the preceding two years, when lying on his left side, he had ex-

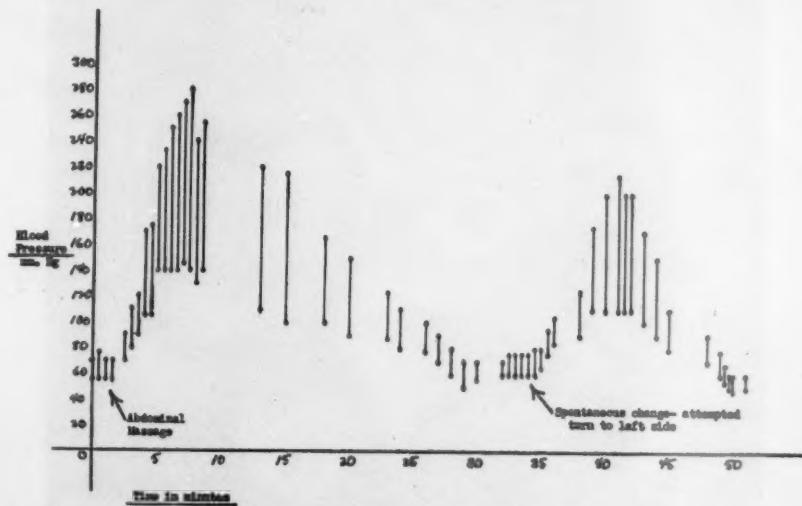


FIG. 1. Blood pressure elevations after abdominal massage and after change in position.

perienced a "gas" pain, which would start in his lower abdomen and fill up the pit of his stomach; it would travel up to his throat and make him feel as though he could not catch his breath. This pain would move to the back and top of his head, and become thumping in character; he would feel shaky and sweat, and would have difficulty in sleeping after this.

Digoxin had been discontinued after the sustained improvement following the patient's initial episode of pulmonary edema. However, in preparation of the patient for surgery it was elected to redigitalize him despite the clinical absence of failure. In addition, supplementary cortisone was begun because of a low 17-ketosteroid determination. The preoperative medication included Thorazine and atropine. Intravenous Sodium Pentothal was used for the induction of anesthesia, then Anectine for a short time. Nitrous oxide, oxygen and ether were used briefly, with continued maintenance on the nitrous oxide and oxygen alone. Later, Mecostin was also used. Considerable difficulty was experienced in inserting an endotracheal tube; a number



FIG. 2. Presacral air insufflation with demonstration of right suprarenal tumor.

of attempts were necessary, and it was at this time that the patient's blood pressure rose to the level of 280-300/160 mm. of Hg. Thereafter, until the tumor was removed, his blood pressure ranged between 180-300 systolic and 100-170 diastolic. Before the tumor manipulation the average blood pressure was 216/120 mm. of Hg, and during mobilization, until removal, it was 268/180 mm. of Hg. This elevation persisted despite the liberal use of the adrenergic blocking agents, Regitine and Benodaine, and a ganglionic blocking drug, Arfonad.

After intubation the patient was placed on his left side. A slightly extended right kidney incision was made. After removal of portions of the twelfth and

eleventh ribs, it was necessary to extend the incision superiorly along the paraspinal muscles. The tenth rib was then resected subperiosteally, and the pleural cavity was entered. The incision was then a thoracoretroperitoneal one, which afforded excellent exposure. The tumor was well encapsulated and loosely adherent to the surrounding tissue. It was separated by blunt dissection. A very large vascular pedicle containing several veins and arteries was found. This was clamped and the tumor was easily removed, along with two pieces of normal-appearing adrenal gland which were adherent to the pedicle. As soon as the blood pressure dropped with the clamping of the pedicle, a Levophed infusion was begun to eliminate the deleterious effects of possible hypotension in an already compromised heart. A drain

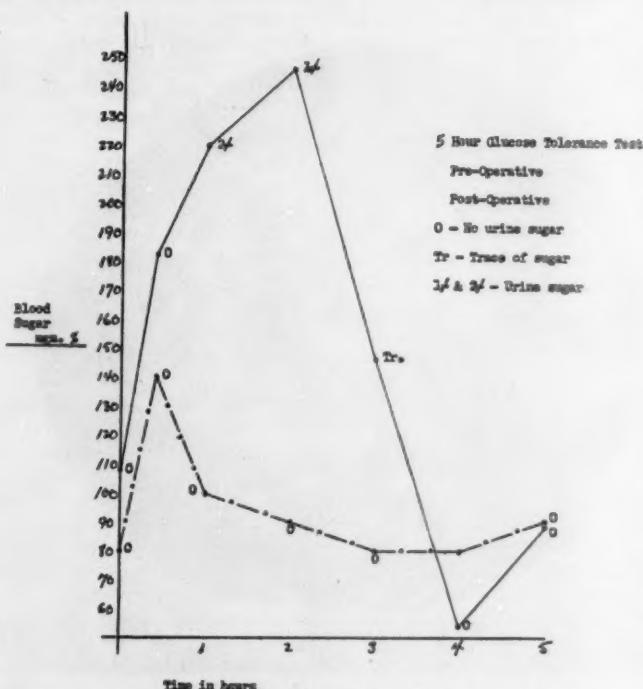


FIG. 3. Preoperative (unbroken line) and postoperative (broken line) glucose tolerance tests.

was placed in the bed where the tumor had lain, and a #20 catheter was placed in the pleural cavity at the eighth intercostal space. This was subsequently connected to underwater suction. After the wound was repaired the patient left the operating room with his blood pressure maintained at 140/80 mm. of Hg. The cardioscope throughout the operation showed a sinus tachycardia and ischemic T waves.

The patient's postoperative course was quite smooth. Levophed was discontinued after 20 hours, and the blood pressure was spontaneously maintained thereafter at an approximate level of 130/70 mm. of Hg. Cortisone was discontinued on the seventh postoperative day, and Digoxin on the eleventh. The thoracic drain was removed on the fifth and the rubber drain the seventh day postoperatively. The

patient was discharged on the forty-seventh hospital day, the twentieth day post-operatively.

Laboratory Data: The initial hematocrit was 48%. However, with better hydration this decreased to 42% by the sixth hospital day. A repeat on the eighteenth day was 32% without any evidence of previous blood loss. Only one of three stool examinations was guaiac positive at this time. The leukocyte count on admission was 14,750, with a slight shift to the left. This had returned to normal by the fifth day, and became elevated only after operation. An initial urinalysis showed one to two white cells, no red cells, negative sugar and albumin, and a specific gravity of 1.018. On the second hospital day a catheter was inserted with difficulty, due to an old stricture. This was kept in place for three days. Subsequent urinalyses

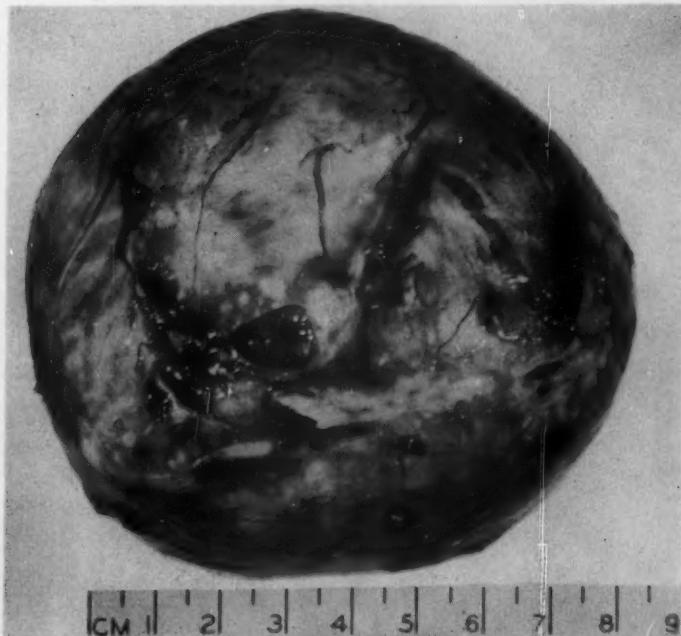


FIG. 4. Right adrenal tumor.

all showed at least a few cellular elements and a trace of albumin. Before discharge zero to two white cells and rare red blood cells were found. On the third hospital day the hemoglobin was 16.0 gm., a sickle cell preparation was negative, a two-hour postprandial sugar was 112 mg.%, and the blood urea nitrogen was 91 mg.%. The latter rose to a peak of 96 mg.% the following day. Serum amylase done on the day of admission was 400 units (normal, 0 to 320), and on the fourth day it was 460 units. Serum lipase done the same day was 1.3 units; bilirubin, 0.812 mg.%. Two blood cultures reported after 14 days were negative. An initial prothrombin time was 82% of normal. On the fifth hospital day no circulating eosinophils were found, calcium was 9.4 mg.%, and phosphorus was 2.6 mg.%. Wassermann test was negative. Studies done on the initial sputum specimens showed a nonspecific growth and were negative for tubercle bacilli. On the seventh day a five-hour glucose tolerance

test showed a diabetic curve (figure 3). Basal metabolism on the tenth day was plus 18%. Repeated electrolyte determinations were all within the normal range except for a sodium of 124 mEq./L. on the fourth hospital day and 128 mEq./L. the first day postoperatively. On the seventh hospital day the serum potassium was 6.0 mEq./L. Sedimentation rates on the eighteenth and forty-fifth days were 27 and 31 mm., respectively.

In addition to the above determinations, a portion of the tumor tissue was macerated and a tissue extract made with an equal volume of water. Epinephrine, 1:10,000, 0.5 c.c., was injected as a control into a dog. It was found that to get a comparable result with our tissue extract it was necessary to use 2.5 c.c. This was compared with tests done on two similar tumor specimens. These showed comparable results to those of the control, with 0.5 c.c. tissue extract and 0.8 c.c., respectively. Thus we had demonstrated a lower epinephrine content in the tumor of our patient than in the others. Quantitative tissue assays for epinephrine and norepinephrine content are now being done by Dr. Marcel Goldenberg at the Columbia-Presbyterian Medical Center in New York City.

Electrocardiographic Data: Initial electrocardiograms showed an incomplete right bundle branch block pattern with marked clockwise rotation. Several hours after admission interference dissociation was present, with abnormal T waves in V2, V3 and V4 indicative of myocardial ischemia. From the second hospital day until the present time, ST elevation has persisted in Leads V2 to V4, the etiology of which is unknown. In view of the fact that we have no evidence for ventricular aneurysmal dilatation, one might postulate that the ST elevation was an has been the patient's normal electrocardiographic configuration all along (no pre-admission tracing ever having been taken), and that the initial tracings with iso-electric ST segments were actually ST depressions and indicative of ischemia. This would actually tend to be confirmed by the postoperative findings given below. Subsequent electrocardiograms showed receding T wave changes with a sinus rhythm. Postoperatively, for one week, the ST segments, previously elevated, were iso-electric, and coved T wave inversion was present from V1 to V4. This was felt to be compatible with myocardial ischemia and right ventricular dilatation.

Radiographic Data: An initial chest x-ray showed cardiac enlargement with pulmonary edema. There was complete regression of the pulmonary edema by x-ray after eight days. An intravenous pyelogram on the twelfth hospital day showed the right kidney to be depressed and rotated. No mass could be outlined. On the nineteenth day a presacral insufflation of 1 L. of oxygen was performed which clearly demonstrated a large suprarenal globular mass pressing on the superior pole of the right kidney. An upper gastrointestinal series on the twenty-first hospital day was normal, without duodenal bulb deformity or displacement secondary to the adrenal tumor.

Pathologic Report: Gross Description: The specimen was a roughly spherical tumor approximately 11 cm. in the greatest dimension and weighing 280 gm. (figure 4). It was completely encapsulated by a fibrous tissue capsule containing rather dilated and sometimes tortuous vessels filled with blood. Numerous yellowish patches, from 2 mm. to 1.5 cm. in the greatest diameter, were visible throughout the capsule. In one area there was definite compressed adrenal cortical tissue, about 1 mm. thick, lying within the capsule. The tumor was fluctuant and quite soft. Multiple cross-sections (figure 5) demonstrated cystic areas containing hemorrhagic fluid. These measured from a few millimeters to 3 or 4 cm. in diameter. The tumor tissue was solid, rather firm, pinkish gray homogeneous tissue, throughout which there were areas of hemorrhage varying from petechial size to several centimeters. Occasional small, yellowish gray patches were noted in the tumor which were somewhat softer and appeared to be areas of necrosis.

Microscopic Description: The tumor was completely encapsulated. It was made up of anastomosing cords of polyhedral cells with rich sinusoids in between. The cells had basophilic granular cytoplasm and vesicular ovoid nuclei. There was mild variation in the size of the nuclei, and giant, bizarrely shaped cells were common (figure 6). There was a distinctly brownish coloration to the Zenker fixed material. Many large areas of hemorrhage were seen. There was a small amount of normal-appearing adrenal tissue on one side.

Diagnosis: Pheochromocytoma, adrenal gland.

Follow-up Data: Since discharge from the hospital the patient has been in good health except for a one-week flare up of epigastric fullness, gas and heartburn seven months postoperatively. This responded promptly to therapy. When seen recently

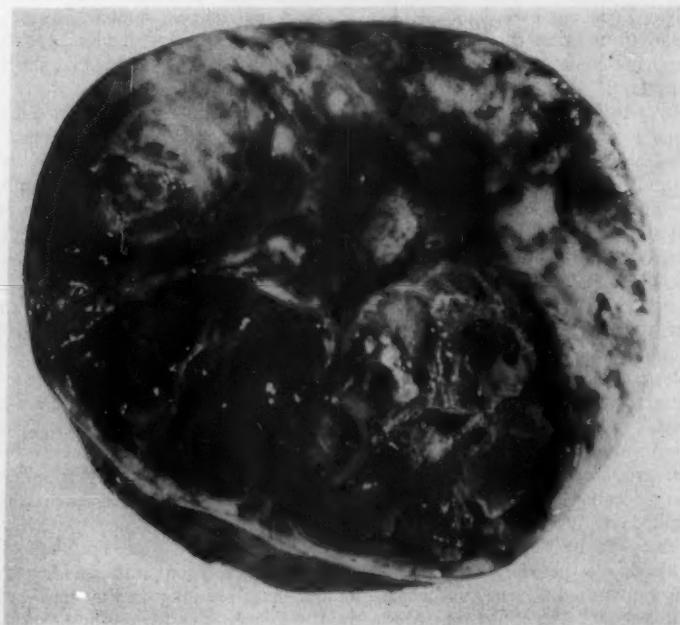


FIG. 5. Cut surface of tumor.

at a nine-month follow-up the patient was asymptomatic and a complete review of his history was undertaken. Since the operation he has not had any "attacks" as previously described. He told us that for two weeks before his admission he had had almost continuous shakiness and tremors of his arms and hands. He dated his stomach trouble as far back as 1939, and said that since that time he had eaten very little meat or greasy foods because they "put gas" on his stomach.

In addition, several important points were brought out. Plain water could cause an episode of epigastric fullness if he drank "too much" of it at one time. This was the same as the distress caused by "too much meat" and greasy foods. He believed this had begun as far back as 1946. Since about 1951 this fullness after drinking water had been associated with a complaint of "misery" extending up into his head, quite similar to the feelings later induced by lying on his left side. Since the operation, for the first time in a number of years, he can drink as much liquid,

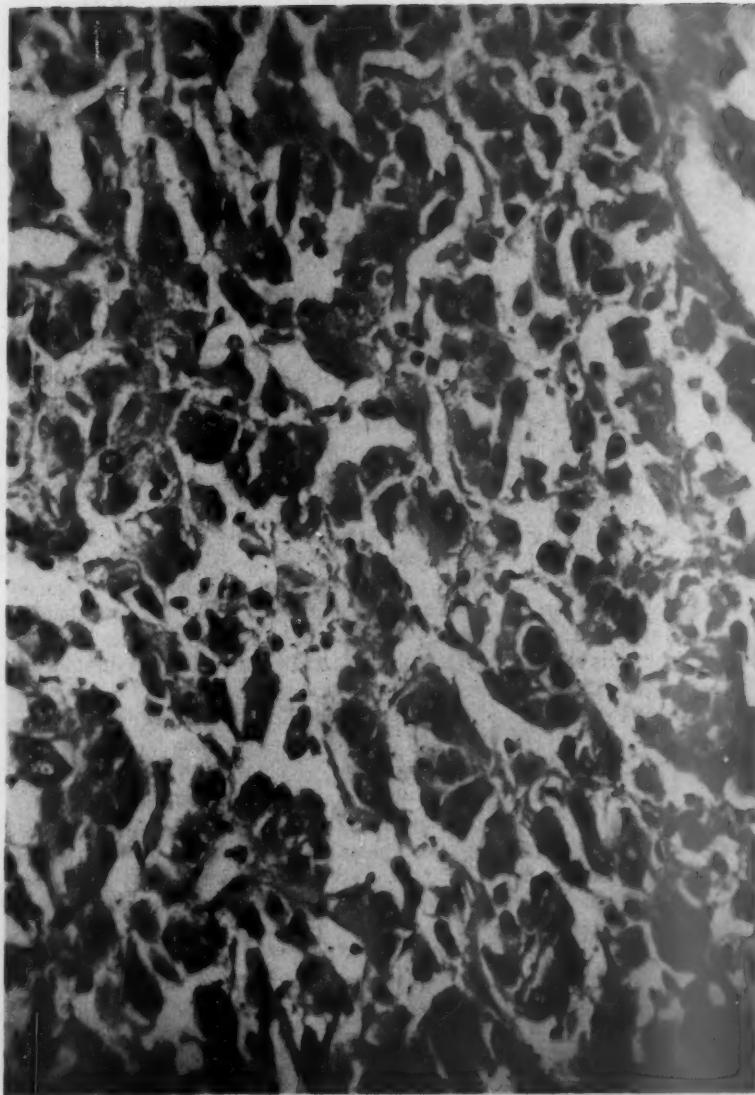


FIG. 6. Microscopic view of pheochromocytoma.

eat as much meat or other food as he desires, and even eat spicy or greasy food without complaints. The patient is now doing his usual work as a janitor. His blood pressure ranges between 110 to 130 systolic and 70 to 86 diastolic. Laboratory data at this time show a hypochromic anemia, occasional white blood cells on urinalysis, and a blood urea nitrogen of 12 mg.%. His basal metabolic rate is plus 10%. Electrolytes and sedimentation rate are all normal. The glucose tolerance test, previously diabetic in character, is normal (figure 3). A 24-hour 17-ketosteroid excretion was 2.2 mg. A chest x-ray and upper gastrointestinal and gall-bladder series were all normal. The present electrocardiogram shows atrial premature beats, left axis deviation, and the elevated ST segments in V₂, 3 and 4 previously mentioned.

DISCUSSION

In retrospect, this case might well be classified in the category of the adrenal-sympathetic syndrome,⁷ especially with the subsequent uncovering of information relating to repeated paroxysmal attacks. This particular aspect of the case is a most important one, emphasizing as it does the difficulty encountered in history-taking, with the further difficulty in subsequent care and treatment of this or any other case. Here, even after the establishment of the diagnosis, when some hint or clue to previous attacks was repeatedly sought, it was only after two weeks that the efforts became fruitful. Unfortunately, when dealing with an acute problem one is faced with the history and physical examination available at the time, and only then is a retrospective view in the making. We knew of no hypertensive attacks, and even the patient thought little enough of the sensations he was experiencing, except for the gastrointestinal symptoms, to seek medical aid, although such was readily available to him. The only symptomatology of which we were aware before his admission was that suggesting ulcer or gall-bladder disease. He had been seen in the health department periodically for these complaints. The exacerbation of his symptoms two months before admission did not respond in the usual manner. It is felt that the symptoms at this time—and possibly for years previously—were not indicative of an ulcer but were related to the effects of postprandial paroxysms, a postulation which seems quite reasonable, and which was proved by the disappearance of his symptomatology following removal of the tumor. In Graham's analysis of 207 cases of pheochromocytoma, three (1.4%) had attacks precipitated by eating.¹ The idea of an active pheochromocytoma with minimal symptomatology of more than a few years' duration would be compatible with the statements in the literature describing only slight attacks,⁹ or the fact that early symptoms are mild and equivocal.¹⁰ In one case report it was felt that the tumor had been present for a period of 20 years.⁶

The presacral air insufflation demonstrated both kidney and adrenal areas very well. It afforded excellent preoperative localization and evaluation of the tumor, and was instrumental in the selection of the approach to be used for its excision. The dangers of such a procedure have often been stressed, but in our case, as in others,⁸ it proved to be both benign and informative.

An explanation for the persistent blood pressure elevation during the operation, poorly controlled by several hypotensive agents, is suggested through the work done by Barnett et al.¹¹—that is, in our use of atropine as a preoperative medication. By the use of norepinephrine alone, and later with atropine, these

authors showed that the combination in normal subjects causes an increase in heart rate and a much greater rise in blood pressure than when norepinephrine is used alone.

SUMMARY

A case of pheochromocytoma which progressed to acute pulmonary edema, operation and clinical cure is presented in detail. A number of well documented paroxysmal hypertensive episodes were recorded. From the history, these episodes had happened on many previous occasions, due to both eating and change in position.

Presacral air insufflation was a benign and valuable procedure in localization of the tumor.

An explanation is offered for the sustained hypertension during surgery.

ACKNOWLEDGMENTS

The author wishes to express his appreciation to Dr. Edward Longabaugh for the surgical care and treatment of this patient, and to Dr. Milton Bohrod for the pathologic report, and to Dr. Leo Cravitz for the qualitative tissue assay for epinephrine content of the tumor.

SUMMARIO IN INTERLINGUA

Un caso de pheochromocytoma es presentate in detallo. Un masculo negre de 41 annos de etate esseva admittite al hospital in acute edema pulmonar. Ille respondeva ben al tractamento usual pro ille condition sed continuava planger se de dolores epigastric. Esseva constatare que su tension de sanguine fluctuava extensemte e que le fluctuationes esseva correlationate con alteraciones de postura. Un pyelogramma intravenose monstrava que le ren al latere dextere esseva deprime e rotate. Un insufflation presacral de aere demonstrava clarmente un grande massa globular in situ suprarenal que pressava contra le polo superior del ren al latere dextere. Esseva effectuate un operation chirurgic. Le tumor esseva excidite. E le paciente se restablia sin incidente. Le reporto pathologic confirmava le impression clinic que il se tractava de un pheochromocytoma.

Le importancia e le difficultate de obtener un accurate historia es signalate. Ab le historia e le subsequente cura clinic in le presente caso il esseva clar que previamente le paciente habeva experientiate episodios del typo describite solmente post mangiar e post biber. Le analyse reportate per Graham super le base de 270 casos de pheochromocytoma monstrava que 1,4% habeva habite attaccos precipitate per ingestion de alimentos. Es sugerite que le tumor habeva essite presente durante plure annos ante le diagnose, con symptomas minimal e attaccos non multo significative. Le test del tolerancia pro glucosa, monstrante un curva diabetic ante le operation, esseva normal al tempore postopératori.

Durante le operation, il esseva constatare que le elevation del tension de sanguine esseva mal stabilisate per plure agentes hypotensive. Es opinare que le uso de atropina como medication preoperatori contribueva a iste difficultate. Le paciente ha notate nulle recurrentia de symptomas e ha habite nulle elevation del tension de sanguine in le curso del novem menses deposit le excision del tumor.

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PRIMARY IDIOPATHIC MYOGLOBINURIA IN A NEGRO FEMALE: ITS IMPLICATIONS AND A NEW METHOD OF LABORATORY DIAGNOSIS *

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INTRODUCTION

MYOGLOBINURIA has been considered to be a relatively rare disease and has been observed only in the white race. Even when the disease is suspected, definitive diagnosis by means of identification of the pigment in the urine has always been a problem. The physician is frequently deterred from further in-

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vestigation because of the difficulty encountered in obtaining laboratory confirmation. Many cases of so-called "march hemoglobinuria" may actually be unrecognized primary myoglobinuria.¹ Several reviewers have questioned the diagnosis of some of the other reported cases of myoglobinuria, and have considered at least some of these cases to be dermatomyositis.¹⁻³

It appears obvious, therefore, that a simple and dependable diagnostic method is needed for conclusive diagnosis.

As the number of case reports and reviews of idiopathic myoglobinuria increase, the use of different terminology causes confusion. All the terms—primary, paroxysmal, spontaneous, familial, paralytic and idiopathic—are being applied to this disease. While any one of these expressions is appropriate in certain cases, it seems reasonable to recommend the use of the general term "primary myoglobinuria" to describe the disease, since this helps to distinguish it from "secondary" myoglobinuria. Myoglobinuria can occur secondarily to some known etiologic factor, such as trauma to a large area of muscle tissue resulting in the crush syndrome.^{4, 5} The "toxic" myoglobinuria, or Haff disease,⁶ severe electric shock,⁷ arterial occlusion with ischemia of large areas of muscle mass,⁸ and possibly dermatomyositis,⁹ are other secondary causes.

The renal complication in myoglobinuria is not always fully appreciated. The primary type of the disease may always be accompanied by some degree of renal damage. Although many of the cases reported in the literature give no specific information concerning renal function, it is interesting to note that approximately one third of the reported cases had evidence of acute uremia. In the remaining cases albuminuria, cast formation and hyperkalemia were frequently noted. Of those who died in uremia, two were autopsied.^{5, 10} The renal lesion was found to be acute tubular necrosis. The case reported in this paper had a renal biopsy which revealed the same diagnosis. One case with uremia who recovered required dialysis on the artificial kidney,¹¹ another required peritoneal dialysis,¹ and our patient also underwent peritoneal dialysis because of hyperkalemia, and survived. Primary myoglobinuria should be kept in mind in the unusual case of acute renal failure.

It is the purpose of this paper, therefore, (1) to present another case of primary or idiopathic myoglobinuria, the first reported in a Negro; (2) to outline a new and relatively simple technic capable of identifying the pigment myoglobin; (3) to stress further the renal complication which is frequently present; and (4) to discuss possible pathogenesis and the nature of the disease myoglobinuria.

CASE REPORT

A 24 year old Negro female was admitted to Grady Memorial Hospital on June 1, 1955, with complaints of generalized myalgia, weakness, and a history of having passed dark urine for three days. There were no other urinary tract symptoms, but feverishness, transient diarrhea and low back pain were noted. There was no history of a previous similar episode in the patient or her family. She denied trauma, excessive physical exertion, or the ingestion of drugs. There was no significant past history other than three term pregnancies complicated by hyperemesis and hypertension. During the last pregnancy a transient episode of jaundice had occurred which was thought to represent infectious hepatitis. The patient had had an appendectomy in 1944.

On admission to the medical service the vital signs were: temperature, 100.2° F.; pulse, 90; blood pressure, 115/90 mm. of Hg; respiration, 16. The patient was moderately obese. She appeared to be in no acute or chronic distress. No jaundice was apparent. The heart, lungs and abdomen were normal. No edema was present. The deep tendon reflexes were somewhat hypoactive, but no muscular weakness could be demonstrated. The physical examination did not reveal any significant findings.

The laboratory studies revealed a hemoglobin value of 14.3 gm., with a packed cell volume of 50%, plasma of normal color, and a white blood count of 9,000, with a normal differential. The urine was scanty in amount, was colored a dark red-brown, and had a pH of 4.5 and a specific gravity of 1.012. There was a 1 plus albuminuria. Microscopic examination demonstrated many coarse granular casts but no cellular elements. The urine gave a strongly positive benzidine test, but tests for bile, urobilinogen, porphobilinogen and homogenetic acid were all negative. The blood urea nitrogen was 51 and the total serum bilirubin was 0.5 mg.%.

X-rays of the chest, kidney, ureter and bladder showed no pathology. Other laboratory procedures performed during hospitalization were: VDRL, negative; Coombs', negative; Donath-Landsteiner, negative. No cold agglutinins were found, and the erythrocyte fragility was within the normal range. Electrophoresis of the hemoglobin showed it to be of the normal adult type.

Hospital Course: On the day of admission it was noted that the patient was severely oliguric. Acute renal insufficiency was suspected, and appropriate treatment was begun. Potassium intoxication became evident on the second hospital day and was brought under control by peritoneal dialysis.²⁴ A normal serum potassium was maintained with cation exchange resin.* Diuresis began on the fourteenth hospital day, and recovery was subsequently uneventful. A renal biopsy performed on the twenty-first hospital day confirmed the diagnosis of acute tubular necrosis.

During the last one and one-half years since discharge the patient has been followed in the outpatient department and has reported at least two other episodes of dark red urine which were not severe enough to cause her to seek hospitalization.

Comment: The clinical course of our patient concurs with the accepted typical picture of myoglobinuria, adequate descriptions of which have been published by others.^{1, 8, 11-18} Most of the patients have experienced an acute onset, with fever, chills and weakness. There may be muscle pain, loss of strength and, in some cases, paralysis, the legs being prominently involved. The upper extremities as well as the tongue, jaws and intercostal muscles may be affected. The urine is noted early to be colored brown to dark red. Evidence of acute renal insufficiency often develops without any obvious precipitating cause. When tubular necrosis is present to the degree that a lower nephron syndrome is produced, red blood cells are also found in the urine, as is frequently the case with tubular necrosis from any cause. The common and highly indicative laboratory findings for primary myoglobinuria are a dark urine with a strongly positive benzidine test but with no red blood cells, no anemia and no hemolysis in the serum. Definitive diagnosis of primary myoglobinuria, however, depends upon positive identification of the pigment in the urine.

SPECIAL DIAGNOSTIC LABORATORY STUDIES

Diagnosis of myoglobinuria has relied mainly on the use of the spectrophotometer and the ultracentrifuge for identification of the pigment in the urine.

* Sodium salt carboxylic acid type resin, furnished by Eli Lilly & Co.

In this case, spectrophotometric examination was performed with the Beckman Model DU instrument, and figure 1 shows the spectrophotometric curves of known metmyoglobin and methemoglobin preparations compared with that of the patient's urine. Pure preparations can be readily identified, but the presence of hemoglobin or of other pigments found in the urine can cloud the spectrophotometric analysis of myoglobin. Ultracentrifugal analysis was carried out using the Spinco Model E Ultracentrifuge. Values obtained for the sedimentation constants agree with the values for myoglobin reported by other investigators (table 1). Urinary proteins may possess sedimentation constants similar to myoglobin, and this possibility confuses the interpretation of ultracentrifugal

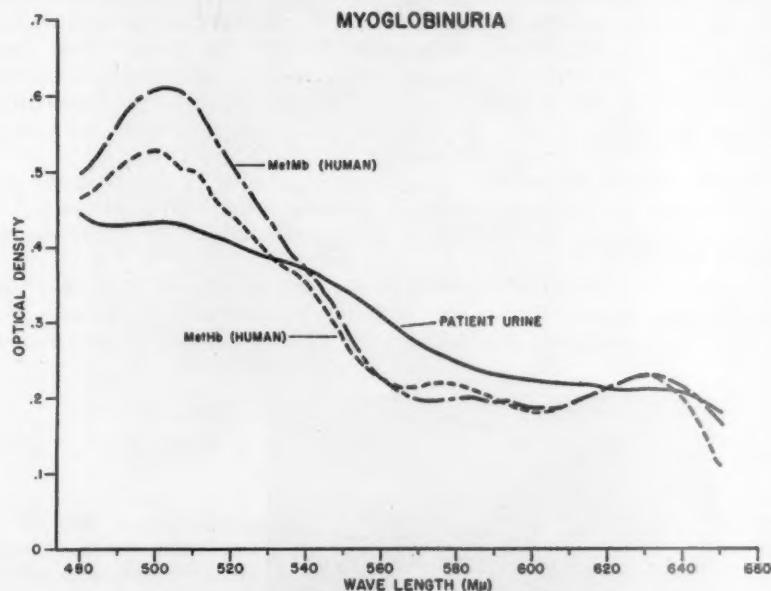


FIG. 1. Spectrophotometric curves of metmyoglobin, methemoglobin, and the patient's urine.

results. Since the evidence obtained with the spectrophotometer and the ultracentrifuge appeared to be compatible with, rather than diagnostic of, myoglobinuria, other means were sought to obtain definitive diagnosis. An apparently specific analytic procedure was devised based upon paper electrophoresis and a special staining technic.

Paper Electrophoresis Procedure for Myoglobin in Urine: Paper electrophoresis was performed at 200 volts for 22 hours using Whatman No. 3 filter paper in pH 8.6 barbital buffer of 0.05 ionic strength. The urine specimen for electrophoresis is prepared by adding one part of a benzidine-positive urine to two parts of a human serum. The serum proteins do not stain with benzidine, but they do prevent myoglobin or hemoglobin from adsorbing to the filter paper.

TABLE 1

Data from the Ultracentrifuge Comparing Myoglobin, Hemoglobin
and the Patient's Urine

| Preparation | S_{20} , Saline |
|---------------------|-------------------|
| Human Hb | 4.6 |
| Beef Mb | 2.0 |
| Patient urine | 2.5 |
| Reported values: Hb | 4.5 |
| Mb | 2.0 |

Serum specimens from patients suspected of having myoglobinuria are examined directly. After electrophoresis the filter paper is removed from the instrument and fixed in the oven at 125° C. for 10 minutes. Stained patterns are obtained by applying a benzidine-hydrogen peroxide solution with a fine caliber glass hand spray. Since only myoglobin and hemoglobin are stained, and myoglobin migrates only half the distance traveled by hemoglobin, definite differentiation and identification are possible (figures 2 and 3). Photography of the stained pattern must be done immediately because decolorization is fairly rapid.

The benzidine-hydrogen peroxide solution is prepared by dissolving 0.3 gm. of recrystallized benzidine in 2 ml. of glacial acetic acid. Two milliliters of 3% hydrogen peroxide are added to the benzidine acetic acid mixture immediately before it is used.

Results: Examination of the urine of the patient with electrophoresis and benzidine stain revealed the presence of both myoglobin and hemoglobin. The mobility of the myoglobin in the urine was the same as that of preparations

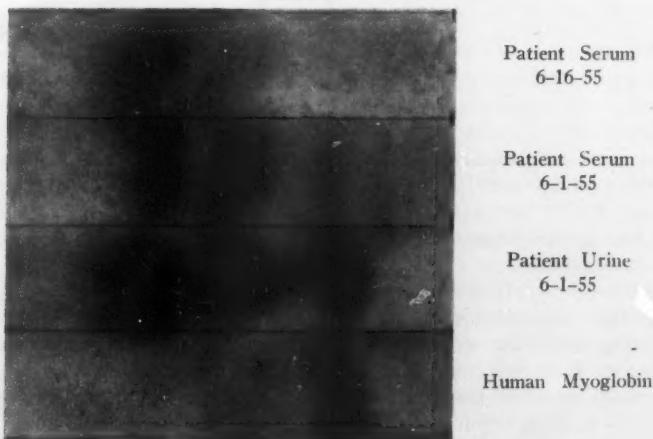


FIG. 2. Electrophoretic pattern of the patient's serum and urine during overt myoglobinuria (6-1-55). Note that the patient's urine and serum also contain hemoglobin and the fast hemoglobin complex (haptoglobin), but that the myoglobin is easily distinguished as it migrates only one-half the distance. Also note that a small amount of myoglobin is detected in the patient's serum by this method. Myoglobin is absent from the serum 15 days later (6-16-55).

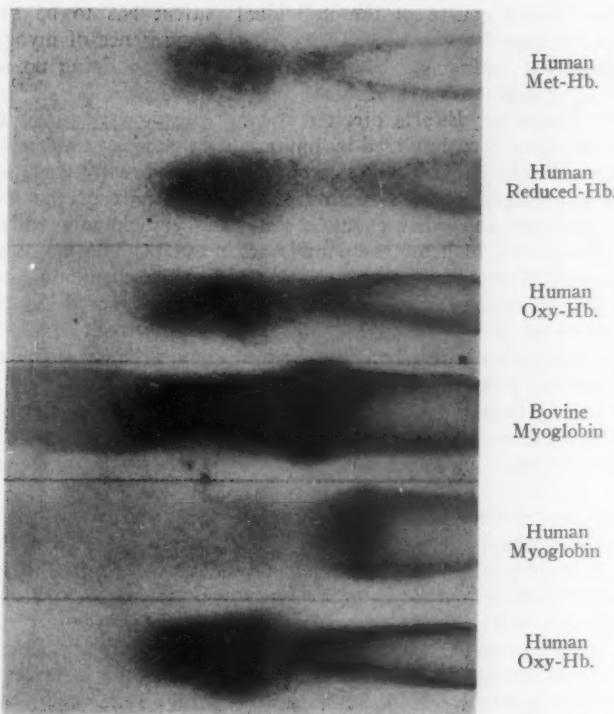


FIG. 3. Electrophoretic pattern comparing human and bovine myoglobin with human hemoglobin in the various forms.

made from human heart and muscle, but not the same as those from beef heart. Analysis of one serum specimen taken during the acute stage revealed myoglobin in the serum of the patient.

DISCUSSION

The patient with primary myoglobinuria not only presents manifold problems in the detection and diagnosis of the disease and in evaluation of complications, but also furnishes a challenge to the investigator with respect to determining the incidence and understanding the pathogenesis and the nature of the disease. Controversial points particularly involve the hereditary background and relationship to the muscle and pigment diseases.

Negro Case: All patients previously reported have been members of the white race. The patient presented in this paper is the first Negro case diagnosed as far as we have been able to determine. This one case makes one hesitant to believe that primary myoglobinuria does not exist in the Negro population. It seems probable that a case of the disease in this race has not previously been recognized.

Detection: Recognition of myoglobinuria requires familiarity with the clinical

picture. The clinical course of the individual patient has to be sufficiently characteristic to suggest a tentative diagnosis. The presence of myoglobinuria should be suspected in any patient with a dark urine containing no red blood cells yet giving a positive benzidine test.

Definitive Diagnosis: Efforts directed toward developing a definitive diagnostic procedure have been hindered by limitations inherent in the usable instruments or procedures. The absorption curves obtained with the spectrophotometer are influenced by the reactions of the heme part of the molecule.¹⁷ Oxygenated, reduced and other complex states of hemoglobin readily confuse the picture if mixtures of heme compounds are present. The major contribution of the spectrophotometer is to prove that a hemelike compound is present. In the case of the ultracentrifuge and paper electrophoresis with the usual protein stains, proteins of the size and mobility of myoglobin can be detected and measured. Uncertainty exists, however, because some urinary, serum and other body fluid proteins possess the same molecular weight and mobility as myoglobin. A highly suggestive, but not definitive, diagnosis can be reached if the spectrophotometer indicates the presence of a hemoglobin-like compound and the ultracentrifuge indicates a substance with a sedimentation constant of about 2.0.

These inherent limitations of the spectrophotometer and ultracentrifuge, plus the fact that the instruments are expensive and require experienced operators, warranted efforts toward developing a simple and definitive diagnostic procedure. This was accomplished because in paper electrophoresis myoglobin migrates at about half the rate of hemoglobin, and because myoglobin can be selectively stained in the presence of serum proteins with a benzidine-peroxide solution. Findings indicate that a detectable level is maintained in the serum only at the height of the acute period, but in the urine for several days.

Pathogenesis: Some observers believe that a predisposing familial^{10, 13, 15, 18, 19} or hereditary factor is present in susceptible persons, and that some trigger mechanism precipitates myoglobinuria. This mechanism has been most frequently reported as strenuous exercise. Some claim that a relationship exists between progressive muscular dystrophy² and primary myoglobinuria, and consider both diseases to be different phases of the same illness.

The idea of a hereditary or genetic basis is well worth considering. Recently, several of the more unusual metabolic diseases have been traced to a single autosomal gene, and may possibly involve a single gene-enzyme-symptom complex.²⁰ In galactosemia²¹ and phenylpyruvic oligophrenia,²² single enzyme systems have been implicated as the basic defect, and the existence of heterozygous carriers has been described. It is possible, although purely speculative, that primary myoglobinuria represents a genetic defect in the enzyme system of the muscle cell (and possibly other cells), which becomes symptomatic with varying factors in the environment. Further studies upon gene and enzyme chemistry appear to be indicated in the search for the basic defect in myoglobinuria.

Nature of the Disease: The existing knowledge of the nature of the disease may be summarized briefly. It has been accepted that myoglobinuria follows muscle necrosis. Gross myoglobinuria occurs when large amounts of muscle tissue are rapidly destroyed (estimated 200 gm. in the adult).² It is interesting

to speculate, as others¹ have done, that between overt attacks muscle necrosis on a small scale may occur and cause liberation of small amounts of myoglobin. It has been further pointed out that minute amounts of myoglobin which are not detectable by available methods may be released in the various myopathies. By means of specific staining of the electrophoretic pattern, myoglobin was detected in the apparently clear serum of our patient during the time that gross myoglobinuria was present, but not after gross myoglobinuria had subsided. The relationship of primary myoglobinuria to the muscular dystrophies is not clear at present, especially in regard to the microscopic picture of muscle tissue in the two conditions.²

It has not yet been conclusively demonstrated that urobilin, creatine, uroporphyrin or even hematin is the direct consequence of the *in vivo* destruction of released myoglobin.¹⁷ It is to be expected that substances³ besides myoglobin will be released into the circulation when muscle tissue is destroyed. Creatine is one substance which has frequently been found elevated in the sera of these patients. If renal damage of severe degree is present, one would expect to find these substances in high concentration in the serum, but the released enzymes appear to be disposed of in ways other than by renal excretion. Lactic and pyruvic acid release evidently follows muscular exertion, and not muscle necrosis. It has been implied that some of the products of muscle breakdown are toxic to the body,⁸ but this seems unlikely in the concentrations in which they are present.

There is no evidence to support the concept that the myoglobin of the patient with primary myoglobinuria is an abnormal type of myoglobin. In a recently reported study, as well as in our case, no difference was detected between the myoglobin of the patient and that of a normal control preparation made from human tissues by means of electrophoretic examination.²³ The existence of fetal myoglobin has been demonstrated,^{24, 25} but has not been implicated in idiopathic myoglobinuria. A species difference was evidenced by our finding that the electrophoretic pattern for beef myoglobin is different from that for human myoglobin.

In summary, although no definite basic defect in primary myoglobinuria can be demonstrated at the present time, a syndrome with a sufficiently consistent clinical and laboratory picture is becoming more frequently recognized. It seems unlikely that primary myoglobinuria is a true variant of any of the now recognized myopathies. The known secondary cases of myoglobinuria are more readily separated from the group. Myoglobin released from muscle tissue in the primary disease is not of the fetal or abnormal type, and there is no evidence that substances released into the circulation along with myoglobin are harmful in themselves. It is suspected that defective genes and deficient enzymes may be involved in myoglobinuria.

Renal Complication: The patients who succumb to myoglobinuria die in acute uremia, and the renal lesion responsible is acute tubular necrosis (lower nephron nephrosis).⁵ Varying degrees of tubular damage occur with different paroxysms, and may vary from frank renal insufficiency to occult findings requiring inulin and para-aminohippuric acid clearance and maximal tubular excretory capacity studies for their detection. The implications of this are twofold:

(1) the chance is excellent that a patient with paroxysmal myoglobinuria will develop acute renal insufficiency, and (2) repeated attacks of myoglobinuria may predispose to chronic renal failure over a period of years. This latter statement is somewhat intriguing, but of course is only speculative.

The explanation for the occurrence of renal damage with the excretion of myoglobin, hemoglobin or any other type of pigment is highly controversial. Experimental attempts to induce renal damage with all types of pigments have produced confusing results but, with only two exceptions, clear-cut evidence of renal damage has not been found. Flink²⁶ injected massive amounts of hemoglobin into dogs (4 to 6 gm./Kg.) and obtained renal damage only with an average plasma concentration of over 2.2 gm./100 c.c. Only at this exceptionally high level did azotemia, albuminuria and cast formation occur; however, urine volume remained high, suggesting that the lesion was not identical with human cases of acute tubular necrosis. Hematin,²⁷ when given in doses of 23.7 mg./Kg. or greater, has proved to be quite toxic to the tubules.

In interpreting published experimental data, one should remember that many of the experiments using hemoglobin and myoglobin have been performed with rabbits, an animal which has essentially no myoglobin in the muscle and possesses a notoriously labile sympathetic system. The state of hydration, allergic reactions and increased sympathetic activity which may have resulted in renal vasoconstriction and in a reduction of the glomerulofiltration rate were not evaluated in these experiments. However, in almost every instance in which a markedly reduced filtration rate was produced during injection of the pigment, a lesion of tubulorrhexis developed.²⁷

Oliver's^{28, 29} work in the correlation of the pathology and physiology of acute renal failure contributed greatly to better understanding of this condition. He described two types of tubular lesion: (1) the nephrotoxic, and (2) the tubulorrhoxic (anoxic). It is doubtful if either of these lesions occurs alone. Oliver demonstrated by his dissection technic that even in mercury poisoning a patchy focal cortical ischemia occurs, and that the final result is a mixture of the two lesions, even though no frank shock was present. It is certainly not inconceivable that renal ischemia can occur without peripheral circulatory failure in a disease like myoglobinuria.

Therapy: Satisfactory treatment and prevention of myoglobinuria in the individual patient cannot be accomplished until a better knowledge of the mechanisms of the disease is obtained. Therapy at present consists of avoiding strenuous exercise when it appears to be a precipitating factor, and of treating the acute tubular necrosis properly when it is a complicating factor.

SUMMARY

A case of primary myoglobinuria occurring in a 24 year old Negro female has been reported. Diagnosis was confirmed by a new and more sensitive method for the identification of myoglobin in urine and serum, employing paper electrophoresis and a peroxide-benzidine stain. The primary type of myoglobinuria has been discussed and attention drawn to the fact that acute renal insufficiency is a common complication.

SUMMARIO IN INTERLINGUA

Myoglobinuria primari o idiopathic, un morbo rar que ha previemente esseva reportate solmente in subjectos de racia blanc, esseva observata in un feminina negre. Iste morbo differe ab le myoglobinuria que resulta ab un cognoscite factor etiologic, como per exemplo le syndrome de contusion, morbo de Haff, choc electric, o occlusion arterial associate con ischemia de extense areas de massa muscular. In le caso del paciente hic describite, le diagnose esseva sugerite per su historia clinic; illo esseva establete per le identification positive del pigmento in le urina e le sero per medio de un application special de electrophorese a papiro.

Le paciente in question, un negra de 24 annos de etate, esseva hospitalisate con gravamines de myalgia generalisate, debilitate, e un historia de tres dies de urina de color obscur. Le die de su hospitalisation, le paciente esseva severamente oliguric. Subsequentemente, un biopsia renal demonstrava le presentia de acute necrosis tubular. Le tractamento consisteva del mantenentia de un appropriate balancia de liquido e de dialyse peritonee pro intoxication per kalium. Le restablimiento se faceva sin incidente.

Le information obtenuite per medio de spectrophotometria e ultracentrifugation non esseva diagnostic sed se trovava in harmonia con le presentia del pigmento myoglobin in sero e urina. Le prova positive esseva obtenuite per tinturar electrophoretogrammas con benzidina e peroxydo de hydrogeno. Le technica usate in iste manovra esseva le sequente:

Electrophorese a papiro es effectuate a 200 volt durante 22 horas con papiro-filtro Whatman No. 3 in tampon de barbital a pH 8,6 e un fortia ionic de 0,05. Le specimen de urina pro le studio electrophoretic es preparate per adder un parte de urina positive pro benzidina a duo partes de sero human. Le proteinas seral non es tinturate per benzidina sed illos reduce le adsorption del myoglobin o de hemoglobin al papiro-filtro. Specimens de sero ab patientes suspecte de haber myoglobinuria es examinete directemente. Post le electrophorese, le proteinas in le papiro-filtro es fixate per le exposition durante 10 minutus a un calor de 125 C. Le tinturation del configurationes es effectuate per applicar le solution de benzidina e peroxydo de hydrogeno per medio de un aspergitor manual de vitro a calibre fin. Viste que solmente myoglobin e hemoglobin es tinturate e que myoglobin migra solmente un medietate del distantia migrate per hemoglobin, il es clar que differentiation e identification positive es possibile. Le configurationes debe esser photographate immediatamente post lor tinturbation proque le discoloration procede satis rapidemente.

Le solution de benzidina e peroxydo de hydrogeno es preparate per solver 0,3 g de recrystallitate benzidina in 2 ml de acido acetic glacial. Duo millilitros de 3 pro cento de peroxydo de hydrogeno es addite al mixtura de benzidina e acido acetic immediatamente ante que illo es usate.

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ADULT ENDOCARDIAL FIBROELASTOSIS: REPORT OF A CASE MIMICKING MITRAL STENOSIS *

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ENDOCARDIAL thickening by excessive fibrous and elastic tissue proliferation in infants and young children with enlargement of the heart and congestive failure is now a fairly well recognized clinical entity.

The concept of prenatal infection as an important cause of such cardiac anomalies was introduced by Kreysig,¹ and the etiologic relationship of "fetal endocarditis" to this endocardial thickening was not seriously questioned until a review by Pototschnig² suggested that the fibroelastic tissue overgrowth was a noninflammatory process. The problem was carefully investigated by Gross,³ who concluded that the lesion should be viewed as a disorder of development. Since then it has generally been considered to be such. The term "endocardial fibroelastosis" was suggested by Weinberg and Himelfarb⁴ to include cases previously reported under a variety of titles; on the basis of 150 cases collected from the literature Dennis and his associates⁵ were able to classify and describe the clinical appearances of the disease. A similar record of the common pathologic changes was made by Gowing.⁶

The first occurrence of what seems quite clearly to be this disorder in an adult was reported by Comeau,⁷ and a collection and analysis of 23 similar cases have recently been made by Guraieb and Rigdon.⁸

A pathologically related disease occurring in adults has been reported with some frequency, principally from Africa. These cases have been sharply demarcated from endocardial fibroelastosis by Thomas and his associates,⁹ who note that they tend to show destruction of endocardium and disruption of elastic framework by a replacing fibrosis, rather than the more uniform overgrowth by both fibrous and elastic tissue components characteristic of fibroelastosis. Termed "endomyocardial fibrosis" by Williams and his co-workers,¹⁰ these cases bear considerable resemblance to the "endocarditis parietalis fibroplastica" described by Löffler^{11, 12} and the "constrictive endocarditis" noted by McKusick and Cochran.¹³ Cases reported by Gray,¹⁴ Levy and Rousselot,¹⁵ Smith and Furth,¹⁶ Fienberg and Holzman,¹⁷ Dammin, Glaser and Roberts¹⁸ and Clark, Valentine and Blount¹⁹ may possibly fall into this category also.

Another group of cases^{7, 8, 9, 20, 21} without endocardial destruction, but with clear proliferation of elastic tissue as well as of fibrous elements, seems more closely akin to the endocardial fibroelastosis of children, and it is to this group that the present case seems to belong. It is of particular interest in the degree to which it simulated mitral stenosis, suggesting the existence of a difficult if infrequent problem in differential diagnosis.

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CASE REPORT

The patient was first seen in the fall of 1952 when, at age 20 years, he was classified 4-F on Army physical examination because of cardiac enlargement noted by x-ray. He was free of cardiorespiratory symptoms and reported that his general health had always been good. Both parents were living and in good health, though his mother was said to have had rheumatic fever as a child. Four brothers and one sister were in good health, but two other brothers were said to have had hypertension. His maternal grandmother had died at 40 of rheumatic heart disease, and a paternal uncle at 47 years of a "heart attack." There was no other history of disease of heredofamilial significance. Though always of small frame, the patient had grown and developed normally, and there was no history to suggest past acute rheumatic fever. He had been quarterback of his high school football team, done outdoor utility work, and passed rigorous National Guard basic training without difficulty.

This first physical examination revealed only these significant findings: moderate bulging of the left chest wall, with angulation of the left costal cartilages (said to have been present since an automobile accident in 1950), and a second pulmonic sound which, while not thought to be unduly accentuated, was louder than the corresponding aortic sound. There were no murmurs. The pulse was regular at 80 beats a minute, and the blood pressure was 120/80 mm. of Hg. The electrocardiogram (figure 1) showed inverted P waves with a short P-R interval in Leads II, III and aVF, indicating "coronary sinus" rhythm. There were prominent S waves in Leads I and II and in all precordial leads, with high voltage QRS complexes in the latter. An orthodiagram showed the transverse diameter of the heart to be 5 mm. less than the predicted value of Ungerleider.²² It was felt at the time that a diagnosis of organic heart disease was not warranted.

The patient remained well until March, 1953, when he noted the abrupt onset of palpitation, of which he was to a greater or less degree aware for the rest of his life. In May, 1953, while engaged in strenuous activity, he was seized with sharp, continuous pain in the left arm. On examination the arm was white and pulseless, but one hour after the onset of the attack a sublingual tablet of nitroglycerin gave immediate relief from pain and produced a return of pulsation. The patient was first given digitalis at that time, which he continued to take for the rest of his life. During the following year he was quite well, but gradually developed shortness of breath on more than usual physical exertion. In the spring of 1954 he began to experience short episodes of extreme respiratory difficulty. These usually occurred while at rest or during sedentary activity, and his exercise tolerance changed very little. At about the same time he began to be troubled with a variety of gastrointestinal symptoms: frequent belching, occasional nausea and vomiting, and episodes of abdominal pain. He had no hemoptysis, cough, nocturnal dyspnea, chest pain or peripheral edema.

In January, 1955, the patient was admitted to the Massachusetts Memorial Hospitals for the first time for cardiac catheterization. He was just under 23 years of age. His height was 5 feet, 7½ inches; his weight, 152 pounds. He was normally developed and appeared to be well. His blood pressure was 110/78 mm. of Hg. There was no cyanosis or clubbing, and the neck veins were flat. The lungs were clear and resonant throughout. There was moderate prominence of the left anterior hemithorax. The heart was enlarged; a maximal impulse of normal force was felt about 1 cm. to the left of the midclavicular line. The heart action was grossly irregular at 80/minute at rest and 120/minute after slight exercise. The second pulmonic sound was louder than the second aortic, but no murmurs were heard. No abdominal organs or masses were felt, the genitalia were normal, and the neurologic examination was within normal limits. There was no edema, and peripheral

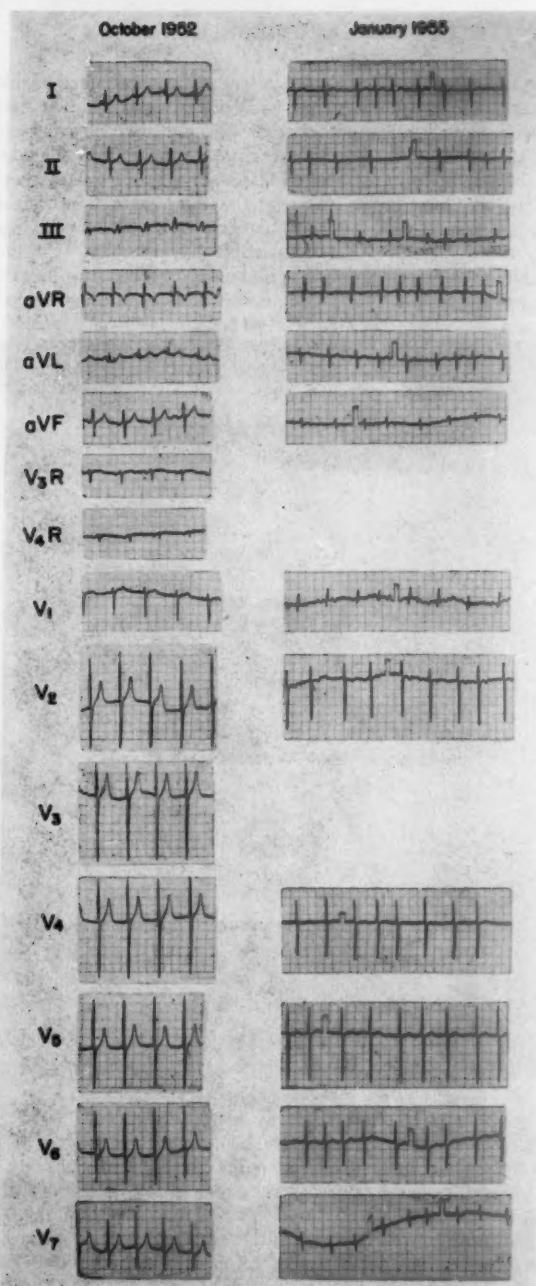


FIG. 1. Comparison of electrocardiograms taken when patient was first seen and at the time of operation, showing the development of a QR deflection in V₁ and deepening of the S in Leads I and aVL. (Tracings retouched.)

pulses were all present. The blood urea nitrogen was 16; fasting blood sugar, 98 mg.%. The hemoglobin was 15.5 gm.%; white blood count, 11,000/mm³. The urine was not remarkable save for the presence of a 1 plus reaction for albumin. Chest x-ray (figure 2) showed a cardiothoracic ratio of 17.5:27.3. There was marked enlargement of the left atrium, as well as lesser degrees of enlargement of the right ventricle and right atrium. There was no pulmonary arterial prominence, but there was generalized pulmonary vascular accentuation. An electrocardiogram (figure 1) showed atrial fibrillation with right ventricular hypertrophy. Cardiac catheterization (table 1) demonstrated elevation of pulmonary arterial and pulmonary capillary ("wedge") pressures, thought to be due to obstruction in the region of the mitral

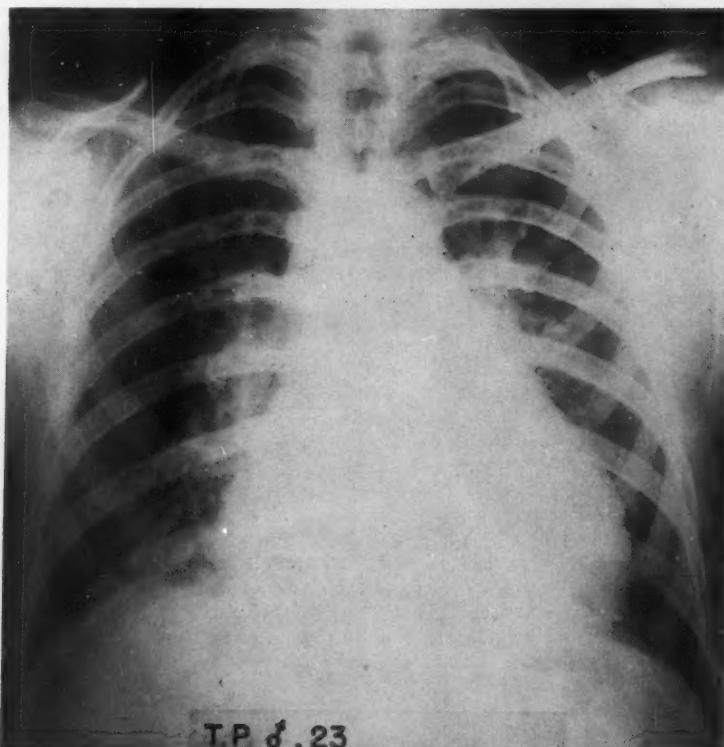


FIG. 2. Chest x-ray taken at the time of operation, showing general enlargement of the heart with prominence of the left atrium.

valve, i.e., mitral stenosis, and associated pulmonary vascular disease. Paired blood sample studies showed no evidence of intracardiac shunt, and it was felt that he had rheumatic heart disease with mitral stenosis and atrial fibrillation.

The patient did fairly well at home until about eight weeks after discharge, when one evening he noted the sudden onset of coldness, numbness and "paralysis" of his left leg. On admission to the hospital his pulse was 124/min. apical and 80/min. radial. Physical examination was otherwise unchanged from his first admission except for decreased skin temperature and slight pallor of the lower two thirds of

the left lower extremity, reduced left femoral arterial pulsation, and absent popliteal, posterior tibial and dorsalis pedis pulsations on the left.

The patient was treated with continuous procaine spinal anesthesia for 24 hours, with prompt return of normal circulation, and with heparin for two weeks thereafter. Because of the presumptive diagnosis of rheumatic heart disease with atrial fibrillation and the history of two episodes of embolization, it was felt that surgical correction of mitral stenosis was indicated, and this operation was undertaken on the sixteenth hospital day.*

At the time of surgery the left ventricle was not thought to be enlarged, but was the seat of an easily palpable systolic thrill. No diastolic thrill was felt. The right ventricle seemed somewhat enlarged and the left atrium dilated. The left atrial pressure was 320 mm. of water. No thrombi were discovered on entering the heart, and by palpation the mitral valve was found to be normal, as were the orifices of the pulmonary veins. A biopsy was taken from the left auricle and from the left lung,

TABLE 1
Cardiac Catheterization Data

| | Rest | Exercise |
|---|------------|------------|
| <i>T. P., Male, 22 Years, January, 1955:</i> | | |
| Oxygen consumption (ml./min.) | 273 | 640 |
| A-V oxygen difference (vol. %) | 6.35 | 11.45 |
| Arterial oxygen saturation (%) | 96 | 95 |
| Hematocrit (%) | 41 | 41 |
| Cardiac output (l./min.) | 4.30 | 5.59 |
| Cardiac index (l./min./M ²) | 2.40 | 3.12 |
| Heart rate (beats/min.) | 80 | 126 |
| Stroke index (ml./min./M ²) | 30 | 25 |
| <i>Pressures (mm. Hg)</i> | | |
| Pulmonary artery (syst./diast./mean) | 70/50/60 | 85/55/70 |
| "Pulmonary capillary" (mean) | 28 | 30 |
| Right ventricular end-diastolic | 5 | 12 |
| Brachial artery (syst./diast./mean) | 120/80/100 | 130/95/105 |
| <i>Resistances (dyne sec. cm.⁻⁵)</i> | | |
| Total pulmonary | 1115 | 1000 |
| Pulmonary arteriolar | 595 | 572 |
| Total peripheral | 1860 | 1500 |

which had appeared to be definitely diseased grossly, with marked nodular fibrosis. On microscopic examination the auricular appendage revealed hypertrophy of the myocardium with subendocardial fibrosis, and the lung showed pulmonary arteriosclerosis with atelectasis and epithelial hyperplasia of terminal bronchioles. The postoperative course was uneventful, and the patient was discharged on the twenty-seventh day with the presumptive diagnosis of endocardial fibroelastosis.

He did fairly well at home following the operation for about 10 days but then developed nausea, vomiting, apprehension, sleeplessness, intermittent chest pain and ankle edema. He was re-admitted to the hospital, where it was discovered that he had not taken digitalis since his discharge two weeks earlier. He had uncontrolled atrial fibrillation at a rate of $\pm 180/\text{min}$. and 1 plus edema over the ankles, and had gained five pounds since discharge. He responded well to redigitalization and a single injection of mercurial diuretic, and was discharged after five days.

* Operation performed by Dr. John W. Strieder, Professor of Clinical Surgery, Boston University School of Medicine, and Visiting Surgeon in charge of Thoracic Surgery, Massachusetts Memorial Hospitals.

For the next eight months the patient was followed at home by his family physician and remained relatively well on treatment with digitalis, phenobarbital and intermittent mercurial diuretics, as well as a short course of cortisone therapy. About a month before his final admission he experienced the gradual onset of more marked shortness of breath, ankle edema, postprandial nausea and vomiting, weight loss, restlessness, insomnia and weakness. In spite of increased digitalis and frequency of mercurial injections, these symptoms all became progressively more severe, and he was admitted to the Massachusetts Memorial Hospitals for the fourth time. He did not have orthopnea, paroxysmal dyspnea or chest or abdominal pain, and his bowel habits had undergone no change. His pulse on admission was 108/min. at the heart apex, 60/min. at the wrist and irregular. He was afebrile, and his blood pressure was 120/75 mm. of Hg. He appeared to be chronically ill. He was thin, pale and anxious, and in moderate respiratory distress. The neck veins were not distended, and the lungs were clear and resonant throughout, save for a very few fine, moist râles at the left base posteriorly, which did not clear with cough. The heart was enlarged, the apex impulse strongest in the fifth interspace, about 3 cm. to the left of the midclavicular line. The right border was not percussed beyond the right sternal edge. The second sound was accentuated in the pulmonic area, and a short, sharp systolic murmur was heard at the apex, with moderate transmission toward the heart base and left axilla. The abdomen was not tender, bowel sounds were normal, and no organs or masses could be palpated. There was 2 to 3 plus pitting edema of the feet and ankles. Neurologic examination was not remarkable.

The hematocrit was 55%; white blood count, 6,100/mm.³, with 84 polymorphonuclear leukocytes, 10 lymphocytes and 6 monocytes. The urine was not remarkable save for 2 plus albuminuria on two occasions. A stool was negative to guaiac reaction. The blood urea nitrogen was 27 and the creatinine 0.9 mg.%. Sodium was 131; potassium, 4.9; CO₂, 26.1; chloride 96 mEq./L. Total protein was 5.1; albumin, 1.9; and globulin, 3.2 gm.%. The arm-to-tongue circulation time was 47 seconds; venous pressure, 120 mm. of saline. An L.E. preparation was negative; serum cholesterol was 151 mg.%.

The pulse was controlled with digitalis, but diuretic response to mercurials was poor, and there was only modest improvement in the patient's general condition. Apprehension and sleeplessness were partially allayed with barbiturates and chloral hydrate. Anorexia with occasional nausea and vomiting was a problem in the hospital, as it had been at home.

During the evening of his eleventh hospital day the patient complained of nausea, and 30 minutes later had an episode of vomiting, followed shortly by two bouts of shaking chills. The rectal temperature was 100.8° F. and rose in the next hour to 101.8° F. Dyspnea became more marked, and cyanosis developed. There were dry inspiratory râles at both lung bases, without dullness. There was no flank tenderness, and one urine showed only occasional white and red blood cells. There was slight abdominal guarding, but no pain or tenderness. Bowel sounds were normal, and rectal examination was not remarkable. The liver edge could be felt at the right costal margin. The white count was 20,000/mm.³. Nose, throat and blood cultures were taken, and treatment with oxygen and parenteral penicillin and streptomycin was begun. There was only slight improvement during the remainder of the night, and chest x-ray on the following morning showed no change over a film taken four days before. Later in the morning the patient passed a stool composed principally of mucus and red blood. Bowel sounds were diminished, and diffuse abdominal tenderness developed. X-ray of the abdomen revealed an isolated loop of distended small bowel in the left lower abdomen. It was felt that he had suffered a mesenteric embolism, and in spite of his precarious clinical state operation was felt to be imperative. Shortly after bilateral Xylocaine intercostal blocks he became unresponsive,

and neither pulse nor blood pressure could be obtained. Though there was a return of weak apical beat upon attempts at resuscitation, this ceased after 15 to 20 minutes and the patient died.

A postmortem examination was performed. The abdominal cavity contained approximately 300 c.c. of greenish brown fluid. The appendix was injected and indurated. Just proximal to its tip was a small perforation ringed by a 0.4 cm. fringe of soft, yellow, necrotic tissue. The liver was firm and smooth, its edge lying 2 cm. below the right costal margin. The left pleural cavity contained 200 c.c. of serosanguineous fluid and was bridged by a number of dense fibrous adhesions. The right pleural cavity was not remarkable. The pericardial surfaces were smooth and glistening. There was no free pericardial fluid.

The heart (figure 3) weighed 690 gm. Measurements were as follows:

| | |
|----------------------------------|----------|
| Tricuspid valve (circum.) | 12.5 cm. |
| Pulmonic valve (circum.) | 7.5 cm. |
| Mitral valve (circum.) | 12.0 cm. |
| Aortic valve (circum.) | 5.5 cm. |
| Right ventricle (thickness) | 1.3 cm. |
| Left ventricle, apex (thickness) | 0.9 cm. |
| Left ventricle, base (thickness) | 0.9 cm. |

The right atrium and ventricle showed marked hypertrophy and dilatation. The left atrium was moderately dilated, and the left ventricle appeared to be relatively contracted in contrast to the other chambers. The ductus arteriosus was obliterated, and no septal defects or anomalous vessels could be identified. The valve leaflets were uniformly unremarkable. The left atrial and left ventricular endocardium was smooth, white and markedly thickened. Radiating from the apex of the left ventricle was a fine, linear, fibrous infiltration of the myocardium extending from the subendocardial region. The endocardium of the right atrium and ventricle was not remarkable. The coronary arteries were negative. There was soft, degenerated thrombus material in the left atrium adherent to the left atrial wall over a circular area approximately 2 cm. in diameter.

The right lung weighed 640 gm. and the left, 560 gm. They were firmer and less crepitant than normal, particularly the lower lobes. The walls of the small branches of the pulmonary arteries were thickened but were free of thrombi. Both kidneys showed a number of deeply pitted triangular scars characteristic of infarction, and there was marked injection of the distal 2 feet of ileum.

On microscopic examination the subendocardial myocardium of the left ventricle showed increased fibrosis with widely separated muscle fibers. A few scattered lymphocytes were seen. The endocardium was thickened by fibrous tissue to about eight to 10 times normal. No inflammatory cells were seen in the endocardium. In the left atrium, although the endocardium was greatly thickened, subendocardial fibrosis was absent. Verhoeff's stains of the left atrium and ventricle showed a moderate increase in the numbers of endocardial elastic fibers. The coronary vessels showed moderate, patchy intimal proliferation.

The right and left lower lobes of the lungs showed intense congestion of the alveolar capillaries, with free red blood cells and pigment-containing macrophages in the alveolar spaces. There was moderately severe, loose, fibrous thickening of the intima in both large and small pulmonary arteries. Congestive changes were found in both spleen and liver; the kidneys showed areas of fibrosis suggested by the scarred appearance on gross examination.

Sections of the appendix proximal to the perforation showed a dense, thick, fibrous submucosa with narrowing of the appendiceal lumen but without evidence of inflammation of the muscularis. Sections through the perforation at the tip of the

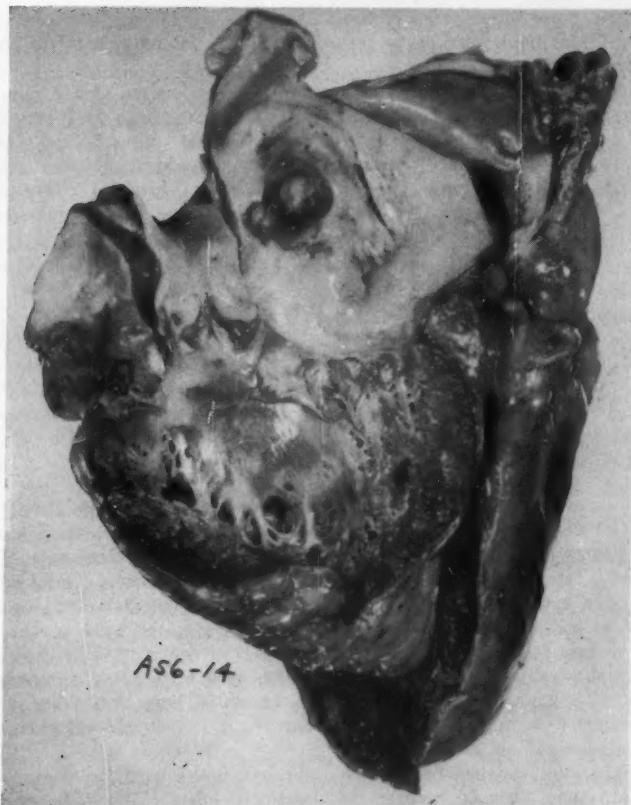


FIG. 3. Heart opened to show thickened left ventricular endocardium and narrowed aortic outlet. In comparison with the greatly enlarged right heart, the left ventricle seems almost contracted.

appendix showed complete replacement of the muscularis by calcium and eosinophilic amorphous material. Without this was a thin congested layer of fibrous tissue showing moderate numbers of neutrophils.

DISCUSSION

The thickening of left ventricular endocardium by fibroelastic tissue overgrowth in this patient strongly suggests a generic identity with cases of endocardial fibroelastosis in children. The reason for the delayed appearance of symptoms in this instance is not evident but it seems reasonable to conjecture that a degree of endocardial disease might exist at birth which would not sufficiently compromise myocardial contraction to cause death from ventricular failure in infancy. Such failure might conceivably be postponed until well into adult life, and in most instances would probably represent a demand on heart muscle overlying the abnormal endocardium which finally could not be met.

While a mechanism akin to the one above presumably played a part in this patient's difficulties, something else seems to have happened which was of even greater importance clinically. In spite of the fact that endocardial disease was confined to the left side of the heart, hypertrophy and dilatation of the ventricle on this side were much less marked than has usually been reported with a similar distribution of endocardial thickening. In contrast, the right ventricle showed striking hypertrophy and dilatation in the absence of rightsided endocardial abnormalities. It seems not unlikely that in this case the impediment to left ventricular filling imposed by the thickened inner wall of this chamber was of relatively greater significance than in similar cases heretofore reported.

Even in retrospect, the information available at the time of operation strongly suggests the diagnosis of rheumatic heart disease with mitral stenosis. While the patient was not known to have had rheumatic fever, there was a positive family history. When he was first examined there was very little evidence for a diagnosis of organic heart disease, but the second pulmonic sound may have been slightly accentuated. Six months later he developed atrial fibrillation, subsequently had two episodes of peripheral embolization, and 18 months later began to have symptoms of congestive failure. A little over three years after his first visit he had definite cardiac enlargement with marked left atrial and right ventricular prominence by x-ray, electrocardiographic evidence of right ventricular hypertrophy and elevated pulmonary arterial and pulmonary capillary pressures on catheterization of the right heart.

While data from left heart catheterization might have pointed away from a diagnosis of mitral stenosis, they could not obviate the necessity for exploratory operation. The etiologic possibilities from preoperative information included left ventricular failure from some unusual cause, mitral stenosis, or constriction of the left ventricle by either epicardial or endocardial disease. At no time during the period of observation was there electrocardiographic or roentgenologic evidence of left ventricular enlargement, so that left ventricular failure of obscure origin seemed unlikely. The only possibility open, if no gradient across the mitral valve existed, would be constriction of the left ventricle by epicardial or endocardial disease, and this could be determined only by inspection of the epicardium.

While patients with tight mitral stenosis in whom no diastolic murmur is heard have been encountered, it is almost certain that at some earlier time a characteristic murmur was present. The fact that this patient was followed through asymptomatic and symptomatic periods without auscultatory evidence of mitral stenosis is an important consideration.

The intracardiac pressure record in this patient revealed some similarities to data obtained by Clark and his associates¹⁹ from a case of progressive heart failure where, though the principal myocardial lesion was one of endocardial thickening by fibrous tissue, there were areas of elastic tissue proliferation. While these authors found pulmonary capillary pressures comparable to those reported above, pulmonary arterial pressures were much lower. This discrepancy seems most probably related to a difference in the severity of the pulmonary vascular changes which may accompany sustained elevation of the left atrial pressure,^{24, 25} and which were quite marked in the patient reported here. An additional factor may well have been the relatively greater degree of concomitant

right ventricular involvement in the cited than in the reported case, but the more recently published report²⁶ of marked pulmonary hypertension in an adult patient with endocardial fibroelastosis confined to the right side of the heart suggests that this may be a less important consideration than is the severity of the pulmonary vascular changes.

The moderate hypoplasia of the aortic valve is not surprising in view of the known frequency with which such anomalies accompany endocardial fibroelastosis.^{5,6}

Though the findings in this patient shed no additional light on the problem of the cause of this disorder, they are in no way in conflict with the concept of responsibility of a fault in development, possibly related to unchecked growth of the proliferating endocardium of the left bulbus cordis, as suggested by Keith.²⁸

The pathologic changes in the appendix suggesting past episodes of submucosal fat necrosis and calcification may have been sufficient to result in rupture of the attenuated appendiceal wall in response only to ischemia or congestion, possibly explaining in part the clinical characteristics of the patient's final illness.

Even though endocardial fibroelastosis has been described only rarely in adults, and even more rarely takes the form exhibited by this case, this disorder might well be considered in patients thought to have rheumatic valvular disease in whom there are atypical findings or in whom characteristic murmurs never appear. The value of left heart catheterization in preoperative investigation of patients with mitral stenosis is illustrated by the findings in this case.

SUMMARY

The case history is presented of a young man who was thought to have mitral stenosis because of the gradual development of cardiac enlargement, atrial fibrillation with peripheral embolization, left atrial dilatation, right ventricular hypertrophy and congestive heart failure. Data from cardiac catheterization supported this diagnosis, but at operation the mitral valve was found to be normal, and postmortem examination following his death from peritonitis due to a ruptured appendix demonstrated only the presence of endocardial fibroelastosis.

The pathology in this case, which was a little unusual, is discussed in relation to the course of his illness.

SUMMARIO IN INTERLINGUA

Il non existe in le litteratura multe reportos de adultos con le hypercrescentia de histos endocardial elastic e fibrose que es characteristic de fibroelastosis endocardial in pacientes de etate pediatric. Le caso hic reportate es illo de un juveme adulto de sexo masculine in qui le lesion mentionate pare haber esseite constatare. Le constataciones clinic resimilava a grados remarcabile le constataciones characteristic de stenosis mitral.

Le paciente esseva primo vidite al etate de 20 annos. Ben que il habeva in su familia un historia de hypertension e febre rheumatic, ille mesme esseva sin symptomas, e le examine physic revelava solmente le presentia de un secunde pulmonic sono cardiac que esseva un paoco plus forte que le correspondente sono aortic. Sex menses plus tarde, le paciente disveloppava fibrillation atrial, e subsequentemente ille experienciava duo episodios de embolisation peripheric. Dece-octo menses plus tarde, ille comenciaava exhibir symptomas de congestive insufficientia cardiac. Un paoco

plus que tres annos post su prime consultation, ille habeva un definite allargamento cardiac, con marcate grados de hypertrofia sinistro-atrial e dextero-ventricular e elevate tensiones pulmono-arterial e pulmono-capillar manifeste in catheterismo dextero-cardiac, sed nulle characteristic murmur mitral diastolic esseva unquam audite.

Un diagnose presumptive de rheumatic morbo cardiac con stenosis mitral esseva formulate e correction chirurgic del condition esseva initiate. Tamen, al operation il esseva constataate que le valvula esseva normal, in despecto del facto que le tension in le dilatate atrio sinistre esseva significativamente elevate.

Circa novem menses plus tarde, le paciente esseva re-admittite—ancora con fibrillation atrial e con sever insufficientia congestive del corde. In le curso del secunde septima de su sojorno al hospital, ille disveloppava vomito, sensibilitate abdominal sub pression, e diarrhoea sanguinose. Esseva opinate que iste phenomenos esseva le efecto de embolismo mesenteric. Le paciente moriva durante le administration de anesthesia in preparation pro un intervention chirurgic de urgencia.

Le examine necroptic monstrava que le causa del morte habeva essite peritonitis in consequentia de perforation del appendice. Le corde pesava 690 g. Atrio e ventriculo dextere monstrava marcate grados de hypertrofia e dilatation. Le atrio sinistre esseva moderatemente dilatate. Le ventriculo sinistre, in comparation con le altere cameras del corde, esseva relativemente contrahite. Le cuspides valvular non esseva remarcabile, sed le endocardio sinistro-atrial e sinistro-ventricular esseva lisie, blanc, e grandemente spissificate. Le examine microscopic provava que iste spissification esseva le efecto de un proliferation histofibrose e -elastic. In le sub-endocardio del ventriculo sinistre, grados considerabile de fibrosis esseva notate sed in sitos plus distante ab le endocardio le affection muscular esseva leve.

Es postulate que in iste caso le importancia relative de un obstruction del efficacia del contracciones sinistro-ventricular esseva inferior al importancia del obstruction imponne in le repletion sinistro-ventricular per le spissificate endocardio e que le evolution de multes del confundente constataaciones clinic esseva influentiate per iste mechanismo inusual.

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ALLERGY TO EFFORT *

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RELATIVELY little has been written in the English literature during the last two decades about any of the physical allergies other than cold allergy. Especially noticeable is the absence of what is spoken of in the French literature as anaphylactic phenomena secondary to effort. It is the purpose of this paper to report such a case. Although it is admittedly an uncommon and not often

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recognized condition, one should be cognizant of its existence as one of the unusual types of physical allergy.

CASE REPORT

A 22 year old white male was admitted to Ireland Army Hospital, Fort Knox, Kentucky, on April 26, 1957, one week after entering the Army. In November, 1948, at the age of 13 years, he had first developed urticaria while playing basketball. Urticaria, and frequently concomitant angioneurotic edema, continued to occur thereafter whenever the patient indulged in any strenuous physical activity, such as handball, basketball, etc. The hives were always generalized in distribution, and the angioneurotic edema was manifested by swelling of his periorbital and perioral tissues, glottic tightening sensation, and edema of his extremities if the reaction was severe. These manifestations usually lasted one to two days before subsiding. The patient had therefore restricted his activity markedly over the several years prior to his induction into the Army.

The patient had first seen his family physician concerning this difficulty in 1949, at the age of 14, at which time routine skin tests showed him to give positive reactions to cat and dog dander, milk, beef, chicken and dust. These tests were positive on passive transfer studies also. However, a history could be obtained of his allergic manifestations occurring after exercise only, no other allergens apparently causing any difficulty. In 1952 the patient was seen by an eminent allergist at a large university medical school where, according to a statement by the patient's family physician, evaluation "confirmed the findings of an exercise type urticaria." The patient was again seen by this allergist on April 10, 1957, at which time scratch skin tests were repeated and were found to be positive to beef, lamb, pork, horse serum, milk, and dog dander. Intradermal skin tests to mixed fungus, grass, and tree pollen were slightly positive. At this time no dermatographia was present before exercise, but "a 2 to 3 plus urticaria factitia was easily demonstrated afterwards." No hives or angioneurotic edema developed during evaluation by this allergist, but the patient stated that the exercise was in the form of running up and down stairs and that he quit when his legs became fatigued, this being prior to the point at which he usually began having trouble. However, he also stated that one month prior to this time he had developed angioneurotic edema of the lip and generalized urticarial lesions after playing handball for a brief period.

Physical examination on admission revealed no abnormalities whatsoever except for a mild dermatographia. Temperature was 98.6° F.; pulse, 80; respiration, 18; blood pressure, 120/80 mm. of Hg.

Laboratory studies included a normal complete blood count, urinalysis and chest film.

During most of the hospitalization the patient's temperature was slightly subnormal, frequently being 97° F. in the mornings.

To reproduce the allergic phenomena, the patient was advised to play basketball for a brief period, after which he developed several urticarial wheals on the torso and angioneurotic edema of the left periorbital tissue. The latter was still visible the following morning, but the urticarial lesions subsided in a matter of a few hours. The patient was subsequently released from the Army.

COMMENT

In 1921 Joltrain¹ first drew attention to urticaria as a manifestation of fatigue. In 1931 Sezary et al.² wrote that Flandin³ had previously described a case of urticaria purpura following movement in 1913. In the English literature Duke⁴ was the first to describe this condition, in his classic paper on

urticaria produced by physical agents. However, his patient reacted not only to physical exertion but also to heat and emotional disturbances.

Following these initial observations much appeared in the literature from 1925 to 1935 concerning physical allergy, most of which was in the foreign literature. However, Duke was prolific^{5, 6, 7, 8} in the English literature during this period. Nevertheless, reports of this particular type of allergy, i.e., allergic manifestations caused by effort, were rare, and as of 1948⁹ only 40 cases had been described in both the English and the foreign literature.* No subsequent cases could be found by the authors on reviewing the recent English literature.

This condition is said⁹ to begin most frequently between the ages of 12 and 50 years. In the case above the patient first noted symptoms at age 13. It is also more frequently found in women than in men.⁹

Although there was no evidence in the above case of heat per se being a contributing or associated factor in producing the urticaria, the role played by heat in the effort urticarial cases has been debated pro and con. Duke^{4, 5, 6, 7} and other American authors¹⁰ have asserted that the two are intimately associated, and that internal heat produced by effort is frequently an associated phenomenon and the subsequent cause of the urticaria. Vaughan and Black,¹⁰ in their textbook on allergy, state that heat sensitiveness is usually present to a certain degree in every case of effort urticaria, and vice versa. However, Kral⁹ contends that such is not the case. He cites as proof cases where effort and cold in one instance¹¹ and effort and perspiration in another¹² had to be present simultaneously to produce the allergic manifestations, while none of the stimuli alone would produce the allergic manifestations. Ordinarily, however, cold deters the appearance of urticaria to effort and heat enhances it.¹³ The factor in favor of those who contend that body temperature plays an important role⁷ is the finding that many of these patients have subnormal temperatures which rise significantly on effort, both physical and mental, prior to the onset of an attack. It will be noted that in our case the morning temperatures were frequently subnormal (97° F.).

The etiology of this condition is unknown. The most logical theory seems to be that of Grant, Pearson and Comeau,¹⁴ who feel that the condition is produced by the release of H-substance or histamine substance by the cells; this, in turn, is produced when acetylcholine is liberated from a nerve ending; finally, it is felt that the nerve stimulus is centrally or reflexly initiated. After an extensive evaluation of a case of heat allergy, Peters and Silverman¹⁵ in 1946 arrived at this same conclusion.

Treatment⁹ of the acute attack is highly successful, but that of the basic condition is poor. Antihistamines in the mild to moderate attack, and intramuscular or intravenous calcium and/or adrenalin in the more severe cases, give good results. In the occasional moribund patient with anaphylactic shock,

* The 40 cases from the world literature reviewed by Kral in 1948⁹ did not include the 22 cases in the report by Sigel,¹⁶ which was published one month prior to Kral's article. In Sigel's report he describes 22 cases of urticaria "caused by heat, exertion, and excitement" seen in Japan during the six-month period from December, 1945, to June, 1946. This, as Sigel himself states, is an extremely large number of such patients to see in such a brief period and "is considered to be unusual." Furthermore, the type of urticarial rash described is somewhat atypical. The information given by this author also implies that all of these patients were allergic to all three physical agents, i.e., heat, excitement and effort. Of some interest, however, is the statement that one of these patients also experienced sensitivity to cold.

even central nervous system stimulants may become necessary. Methods which have been used with only fair success for the basic condition include nonspecific desensitization with sodium hyposulfite, peptones and histamine; desensitization to heat by warm baths, exercises and diathermy; removal of foci of infection, and, finally, steroids.

SUMMARY

1. A case is presented of one of the rarer of the so-called physical allergies—urticaria and angioneurotic edema caused by effort.
2. Some of the more important aspects of the literature on this subject are reviewed.
3. It is the desire of the authors to call attention to an uncommon condition, reports of which have been absent from the English literature for the last two decades.

SUMMARIO IN INTERLINGUA

Durante le passate duo decennios, relativemente paucò esseva scribite in le litteratura de lingua anglese super ulle del allergias physic excepte super le allergia a frigido. De facto, durante le periodo mentionate, il existe nulle reporto del toto relative al allergia a effortio, que es, il es ver, un del typos le plus incomunum de allergia physic. Un caso de iste genero es reportate in le presente articulo.

Le paciente, un masculo de racia blanc de 22 annos de etate, esseva admittite al hospital del garnison a Fort Knox, Kentucky, con un historia de allergia a effortio deposit le etate de 13 annos. Le manifestationes allergic de urticaria, edema angioneurotic, e—in certe casos—edema glottic occurreva initialmente quando le paciente jocava basket-ball e continuava occurrer subsequentemente quandocunque le paciente se permitteva un ardue effortio physic, per exemplo in un sport. Per consequente ille habeva restringite su activitates marcatamente. Le evalutation del caso al hospital revelava solmente le occurrentia frequente de temperaturas subnormal e le disveloppamento de urticaria e edema angioneurotic post le participation in un curte match de basket-ball. A causa de isto, le paciente esseva dimittite ab le armea.

Le existentia de iste condition esseva primo signalate per Joltrain in 1921. Tamen, in 1931 Sezary notava que Flandin habeva describite jam in 1913 le occurrentia de "urticaria purpure post movimento." Post iste observationes initial, multe reportos relative a allergias physic esseva publicate durante le annos ab 1925 a 1935. Tamen, Kral—in 1948—trovava solmente 40 casos de allergia a effortio reportate ante ille tempore in le litteratura de lingua anglese e altere. In un revista del subsequente litteratura anglese nulle cetere casos verificate de iste morbo esseva trovate, ben que Sigel—etiam in 1948—reportava 22 casos de urticaria que ille considerava como causate per calor, excitation, e effortio.

Le condition es plus frequente in femininas que in masculos. Illo comencia usualmente inter le etates de 12 e 50 annos. Le rolo de sensibilitate a calor in illo es controverso. Le majoritate del autores crede que, ben que frigido retarda ordinariamente le manifestation del urticaria post effortio durante que calor lo accelera, certe pacientes es allergic exclusivamente a effortio e non es sensibile pro calor.

Le etiologia del condition non es cognoscite. Le theoria le plus plausibile es que un substantia histaminic es liberate per le cellulas. Isto es producite post le liberation de acetylcholina al terminaciones nerval. Quanto al stimulation nerval, illo es initiate centralmente o per reflexos.

Le therapia del condition fundamental es dissatisfactori, ben que le attaccos acute responde usualmente al acceptate principios de therapia pro iste genero de manifestationes allergic. Dissensibilisation nonspecific per medio de hyposulfito de natrium, peptones, e histaminas; dissensibilisation a calor per medio de banios calide,

exercitio, e diathermia; ablation de focos de infection; e steroides ha essite tentate —con successos non plus que moderate—in le tractamento del condition fundamental.

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HETEROTOPIC BONE FORMATION FOLLOWING SUPRAPUBIC PROSTATECTOMY: REPORT OF A CASE AND REVIEW OF THE LITERATURE *

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INTRODUCTION

HETEROTOPIC bone formation following suprapubic prostatectomy is a clear-cut disorder combining a typical history with certain unvarying physical, roent-

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genologic and histologic findings. Previous reports on this subject have been published almost exclusively in surgical and urologic journals. Since the internist also encounters this rare complication of surgical procedures, it is pertinent that the entity of vicarious bone formation be called to his attention.

The disorder is characterized by development of a flat, bony-hard mass in an incisional site weeks, months or years following prostatectomy or occasionally other surgical procedures. It is usually symptomatic, but not invariably so. The calcific deposit is not painful, but with movements of the abdominal wall it may cause discomfort, since it possesses little flexibility. Moreover, because of its unusual nature, it may confuse the examining physician, suggesting bone tumor, a metastatic growth or a calcified hematoma.

The first report, by Bernasconi,¹ appeared in the French literature in 1912. Nineteen additional cases were reported in the subsequent 36 years, the last patient having been reported by Sewell, Siceluff and Horton in 1948.² Abeshouse³ has reviewed the subject and added an additional case to the total series. This author suggests that the incidence of postoperative heterotopic bone formation is greater following intraperitoneal than suprapubic operations, and that a midline incision is the most usual site for this development. The reasons for its rarity remain a mystery. There appears to be no relationship to genetic factors or to the age of the patient. The present report describes a patient who developed this rare complication.

CASE REPORT

A 69 year old Negro male was hospitalized on the Urologic Service of the University Hospital, Baltimore, Maryland, for a complaint of nocturia six to seven times of about 12 years' duration. The pertinent physical findings were a grade III benign prostatic hypertrophy, hypertrophic arthritis, generalized arteriosclerosis, right inguinal hernia and a moderate hypertension (160/100 mm. of Hg).

On October 31, 1952, two days after admission, a retropubic prostatectomy was performed through a suprapubic incision. The incision was extended through the anterior and posterior rectus sheath. There was difficulty in finding the plane of cleavage between the prostate gland and its capsule. The gland was removed in several fragments, and sharp dissection was necessary to free the glandular tissue from the membranous urethra.

On the first postoperative day there was moderate bloody suprapubic drainage. For four days after operation the patient had fever up to 103° F. Dicrysticin and Terramycin were employed to combat the secondary infection. The subsequent course was uneventful. The histopathologic report confirmed the presence of benign prostatic hypertrophy. The laboratory findings during the period of hospitalization and the subsequent two years were: blood urea nitrogen, 67 to 18 mg.%; total serum proteins, 6.8 to 7.7 gm.%, with a normal A/G ratio; serum calcium, 10.9 to 9.6 mg.%; serum phosphorus, 3.4 to 4.3 mg.%; alkaline phosphatase, 1.6 Bodansky units; acid phosphatase, 0.3 to 0.7 unit.

Four months postoperatively the patient complained of burning on urination and nocturia five to six times. The urine contained numerous pus and red blood cells. Examination at this time revealed a "stony-hard, fixed, rodlike lower midline mass" deep to the suprapubic prostatectomy scar. The patient had noted this mass about a week previously. Roentgen examination showed no evidence of a mass. Stilbestrol therapy was begun on the clinical suspicion of malignancy of the prostate gland with bone metastases. The pain was not alleviated, and in May, 1954, a biopsy of the mass was performed. The histologic report was normal bone. When the patient

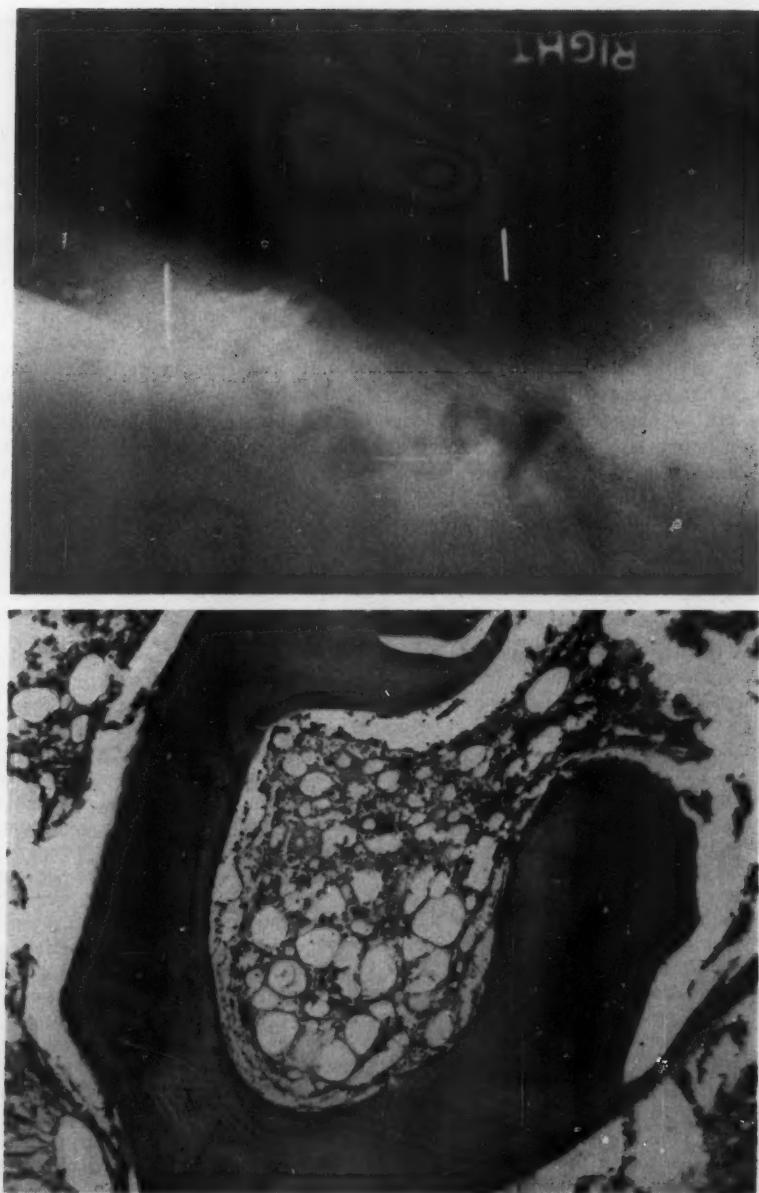


FIG. 1. *Above*, lateral view of abdominal wall showing six inches of heterotopic bone formation between the two white lines. *Below*, microscopic view of biopsy section of heterotopic bone formation showing normal marrow.

was reexamined in December, 1954, he complained of mild pain in the groin. A subsequent x-ray in 1955 revealed a calcific suprapubic mass, 10 cm. in size (figure 1).

DISCUSSION

Heterotopic bone formation following suprapubic prostatectomy has been described as appearing as early as 21 days or as late as 14 years after operation. Maximal growth of bone is usually from one to two months after operation.³ This coincides with Huggins'⁴ experimental findings of osteogenesis occurring 18 to 20 days after transplantation of epithelium from the urinary bladder to the abdominal wall. Most heterotopic bone formation occurs in the linea alba or near the midline of the abdominal wall, usually above the umbilicus and below the lower margin of the sternum, rather than below the umbilical level.^{5, 6, 7} Lyall⁸ stated that ossification of an abdominal scar is usually due to trauma of the lower margin of the sternum or of the upper edge of the pubis. Bone formations have been reported more rarely outside the midline, such as in hernial incisions and in high pararectal incisions. The bone formations following suprapubic prostatectomy have been described as appearing in the posterior aponeurosis of the rectus abdominis muscle above and adjacent to the symphysis pubis and extending down into the prevesical space and attaching to scar tissue arising from the rectus muscles.

Cases of heterotopic bone formation reported following suprapubic prostatectomy, as well as those following other types of operation, were a stimulus to experiments carried on by Abbott and Huggins and their co-workers^{9, 10, 11} and by Weinmann and Sicher.¹² From these studies it was concluded that survival after transplantation of transitional epithelial tissue from the trigone of the urinary bladder of dogs, guinea pigs and rabbits is a prerequisite to the process of ossification in these experimental animals, that it is not the epithelial cells themselves that ossify, but that it is the phosphatic activity of the tissue, muscle or tendon which leads to ossification. This has not been found to occur, however, when the transplant is grafted on such tissue as liver, kidney and spleen, nor will it occur in cases of total parathyroidectomy.¹³ Abeshouse, in his review, points out that it is generally agreed that heterotopic bone formation in man differs pathologically from that obtained by transplantation experiments in animals.

The mechanisms and predisposing conditions underlying the abnormal bone formation are unsettled. Fiddian-Green,¹⁴ in describing a case in which bone formation developed in a wound following pylorectomy for duodenal ulcer, stated that under certain circumstances some cells of the body other than those of the skeletal system assume osteoblastic functions. In the opinion of Villafane¹⁵ and Alves,¹⁶ heterotopic bone formation is a manifestation of a body defense mechanism to surgical or mechanical trauma. Lyall is more specific, and states that when the process occurs in an abdominal surgical scar, it is "usually due to injury of the lower margin of the sternum or of the upper edge of the pubis." Sanders,¹⁷ during seven years, observed six cases of bone formation in upper abdominal scars. The possible causes were (a) heavy labor, (b) inflammation of the wound, (c) constitutional disposition, and (d) periosteal implants because of the riblike appearance and because of proximity or actual attachment to the xiphoid process.

Various authors have considered the factors which must be present when ossification occurs after trauma. Leriche and Pollicard found that bone is formed in connective tissue when edema is present, and that a metaplasia occurs which depends upon two factors: (a) the presence of ossifying fibrocytes, and (b) the proper environmental changes, i.e., an inflammatory reaction or an irritative agent. Lyall regards the osteoblast as merely a specialized type of connective tissue, so that any cell of the mesenchymal series, if placed in a certain physicochemical environment, will tend to produce bone. Thus the above investigators are in agreement with Abbott and his co-workers that embryologic origin alone is not the factor which determines whether bone will form.

In 1954 Loewi¹⁹ reported that after he had implanted bits of urinary bladder from guinea pigs into the chest wall, the abdominal wall, the capsule of the knee joint and the legs of guinea pigs, bone was formed in the granulation tissue surrounding the implanted piece of bladder. The first appearance of bone was noticed in 10 days. However, this did not occur in every animal, and it never occurred in a scorbustic guinea pig. Loewi further found that costal cartilage in contact with implanted bladder showed neither calcification nor ossification. Along similar lines of investigation, Johnson and McMinn,²⁰ using cats, found that homografts were as successful as autografts when bladder mucosa was implanted into the rectus abdominis sheath. They made simultaneous histochemical observations concerning the origin of heterotopic bone formation, and learned that the formation of bone occurs in connective tissue deep to epithelium which has spread from the margins of the graft. This connective tissue showed marked mitotic activity, metachromasia, cytoplasmic basophilia and an intense reaction for alkaline phosphatase. As a result of the work of Alves and Villafane, we find that the other factors bearing on ossification, besides trauma and the presence of granulation tissue, undifferentiated cells and histiocytes, are (a) the mobilization and deposition of calcium, (b) the fixation of vitamin D, and (c) the influence of endocrine factors, especially that of the parathyroid gland. In summary, the chain of events creating the ossification substrate which leads to heterotopic bone formation may be (1) trauma, which stimulates (2) body defense mechanisms in edematous connective tissue and granulation tissue, leading to (3) formation of osteoblasts from histiocytes in (4) the presence of fixed vitamin D and in (5) the presence of mobilized calcium, deposition of the latter being under the influence of (6) the parathyroid gland.

Pasqualetti²¹ observed from his research that the following conclusion can be drawn, i.e., the two theories advanced from osteogenesis (the older osteoblastic cellular and the newer physicochemical-humoral) are perfectly justifiable, and can coexist and explain the formation of bone, although through different modalities.

Can anything of practical therapeutic value be gained from the above noted investigations? In 1956 Rush and Cliffton²² used autogenous bladder mucosa for the reconstruction of tracheal rings in dogs. When the tissue was placed with the mucosal surface away from the lumen it was possible to introduce a satisfactory supporting structure of bone in the surrounding connective tissue, and a complete epithelial lining developed in the tract which was so indistinguishable from surrounding epithelium that its primary origin was difficult to determine. In 1956, also, Hillemand and co-workers,²³ in reporting three cases of

subumbilical ossification of scars following gastrectomy, discussed the use of implants of bladder mucosa in the treatment of pseudarthroses. Thus it can be seen that heterotopic bone formation may not be simply an unpleasant post-operative complication, but may prove to be of constructive value in medical and surgical therapy.

SUMMARY

1. A case demonstrating heterotopic bone formation in a surgical wound has been presented.
2. The subject is reviewed in part as it relates to etiology, incidence and pathogenesis.
3. The significance of heterotopic bone formation is presented, particularly with reference to differentiating it from tumor, metastases, foreign-body reaction and hematoma.
4. The possible value of employing heterotopic bone formation for therapeutic purposes is noted.

SUMMARIO IN INTERLINGUA

In 1911, Bernasconi¹ reportava le prime caso de formation de osso heterotopic post prostatectomia suprapubic. Le caso del presente reporto es le vinti-tercie de su genero in le litteratura medical.

Formation de osso heterotopic pote sublevar problemas de diagnose e debe esser differentiate ab tumor, carcinoma metastatic, reaction a corpore estranie, e hematoma. Illo es un entitate rar e se trova reportate infrequentemente in le litteratura medical. Le majoritate del casos es reportate in publicationes chirurgic e urologic.

Multe recercas ha essite dedicate a determinar le rationes del formation de osso normal in sitos anormal, specialmente in areas incisional postoperatori. Le condition ha essite reproducite in animales experimental. Tal recercas es mentionate, e certe theorias es presentate con respecto al factores etiologic que participa in le formation de osso heterotopic. Iste factores, que concerne le phenomeno del ossification, es (1) trauma le qual produce un stimulation de (2) mechanismos defensive del corpore in edematoso histos conjunctive e histos de granulation con le resultato de (3) le formation de osteoblastos ex histiocytes in (4) le presentia de ficate vitamina D e in (5) le presentia de calcium mobilisate que es deponite sub le influentia de (6) le glandula parathyroide.

Recentemente le reproduction experimental de formation de osso heterotopic ha essite tentate como mesura therapeutic in le tractamento de pseudoarthroses.

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EDITORIAL

RECENT OBSERVATIONS REGARDING THE EPIDEMIOLOGY AND PATHOGENESIS OF SARCOIDOSIS

THE intensive work that has been devoted to the study of sarcoidosis during the past few decades has amassed much information regarding its clinical course and the protean manifestations it may present. But little positive information has been obtained, however, as to its etiology and pathogenesis. The resemblance of the sarcoid nodules to ordinary tubercles attracted prompt attention, and since the early descriptions of Boeck some 50 years ago, many investigators for this and other reasons have supported the view that sarcoidosis is a special type of tuberculous infection. Others have maintained with equal vigor that sarcoidosis is a specific independent disease of as yet undetermined etiology.

Histologically the sarcoid lesions resemble tubercles in many ways. They are compact nodules of epithelioid cells, more or less concentrically arranged, usually containing some giant cells in the center. The nodules are disseminated, often widely, and they may be found in almost any tissue of the body. They may also occur in aggregates which occasionally form large tumor masses. Sarcoidosis usually runs a protracted afebrile course, like a very indolent infection if it be an infection, rarely killing as a result of acute intoxication. The lesions may eventually heal and shrink with considerable scarring. Mechanical pressure from the lesions or distortion from subsequent scarring, however, may cause serious or even fatal local damage, particularly if the lesions involve the eye, the lungs or the myocardium.

There are some significant differences from tuberculosis, however. There is rarely any appreciable inflammatory reaction in or around the sarcoid lesions. There is practically never any notable necrosis although tiny areas of necrosis can occur, and there is no caseation. There are also some differences in the character of the giant cells, which in sarcoid may contain peculiar inclusions not present in tuberculosis. There is some difference in the distribution of the lesions in the tissues, and there is a marked difference in the response to drugs, both to antituberculosis drugs and to the steroids. Thus sarcoidosis rarely involves the serous membranes or the adrenal glands, tuberculosis rarely the eye, the skeletal muscles or the myocardium. Most distinctive, however, is the almost invariable failure, in spite of innumerable attempts to demonstrate tubercle bacilli in the sarcoid lesions, or indeed any other bacterium or living agent, by staining, culture or animal inoculation. It has been suggested without any proof that some special attenuated form of tubercle bacillus is concerned in sarcoidosis, analogous perhaps to BCG. When cultures of tubercle bacilli have been obtained from patients who developed clinical tuberculosis during the course of sarcoidosis, the organisms have been of the usual type.

Sarcoidosis has appeared exceptionally in patients known to have had a tuberculous infection previously. Not infrequently patients with sarcoidosis have developed an active tuberculous infection which quite often has been fatal. In Longcope's review¹ the incidence of such an infection was estimated at 15% to 25% in autopsied cases of sarcoidosis, and a "high incidence" had been reported in most of the published clinical series. Tuberculosis, however, is frequently a terminal infection in other types of chronic illness, like Hodgkin's disease, disseminated lupus or leprosy. The current evidence does not support the conclusion that an indolent "sarcoid form" of tuberculosis has reverted to the usual active progressive type, although the subject still merits further investigation.

Another peculiar relationship between the two diseases is the negative intracutaneous tuberculin reaction given by about 70% to 80% of the subjects with sarcoidosis. The degree of insensitiveness may be extreme. Not infrequently a negative reaction may be obtained with doses as large as 1 mg. and even with 10 mg. or more of old tuberculin. This condition of "anergy" (Jadassohn) has been regarded by some as evidence of an extraordinarily high resistance to tuberculosis, which leads, perhaps by means of circulating antibodies, to destruction of the tubercle bacilli in the sarcoid tissue.² The "tuberculin" so liberated is thought by some to stimulate the production of neutralizing substances and other antibodies and maintain the high resistance. Leitner,³ on the other hand, attributed the anergy to a consumption of antibodies at the site of their formation in the reticuloendothelial tissues by the circulating antigens.

Direct proof of any such mechanisms is lacking. After vaccination with BCG the tubercle bacilli survive in the tissues of patients with sarcoidosis as long as in other subjects. It is difficult or may be impossible to produce or restore a positive intracutaneous tuberculin reaction in uncomplicated sarcoidosis with BCG, but if active tuberculosis does develop later, the usual positive intracutaneous reaction to tuberculin again appears. This cutaneous insensitiveness to extraneous antigens is not restricted to tuberculin but has been observed with histoplasmin, trichophytin and others.^{4,5} The ability to produce antibodies, however, is not necessarily restricted.⁵ The anergy is not specific and resembles that seen, e.g., in Hodgkin's disease, measles and pandemic influenza.

The formation of sarcoid-like nodules of epithelioid cells may be stimulated by the injection of many substances other than tubercle bacilli. Sabin

¹ Longcope, W. T., and Freiman, D. G.: A study of sarcoidosis, Medicine 31: 1-132, 1952.

² Siltzbach, L. E.: Progress in sarcoidosis, Am. J. Med. 22: 841-847, 1957 (Editorial review with bibliography).

³ Leitner, St. J.: Boeck's sarcoidosis (chronic epithelioid-celled reticulo-endotheliosis or granulomatosis), Tubercle 31: 174-183, 1950.

⁴ Friou, G. J.: A study of the cutaneous reactions to oidiomycin, trichophytin, and mumps skin test antigens in patients with sarcoidosis, Yale J. Biol. and Med. 24: 533-539, 1952.

⁵ Sones, M., and Israel, H. L.: Altered immunologic reactions in sarcoidosis, Ann. Int. Med. 40: 260-268, 1954.

et al. 30 years ago showed that phospholipid extracted from dead tubercle bacilli would excite the formation of tubercle-like nodules of epithelioid cells in normal animals, and subsequently similar lesions have been produced by phospholipid from other sources such as normal human serum and egg yolk.⁶ Similar lesions have been produced in patients with sarcoidosis with BCG vaccine and by injections of Kveim's antigen, a heated extract from excised sarcoid tissue which has been used with considerable success as a specific diagnostic aid in sarcoidosis.

Similar lesions may also be produced following the injection or accidental implantation of certain inorganic materials, such as beryllium and particularly quartz (silica). Localized sarcoid-like nodules may develop, as characteristically in normal subjects as in cases of sarcoid. Some have attributed this reaction to phospholipids of the host liberated by macrophages at the site of these foreign particles.⁷ These quartz granulomata may individually resemble those of generalized sarcoid so closely that differentiation solely on a histological basis is uncertain, and other criteria are also needed.⁷

In view of the failure to demonstrate convincingly any specific causative agent in sarcoidosis, the theory has been advanced that the disease depends upon an abnormal reactivity on the part of the host. The anergy to tuberculin could be one manifestation of this, and the development of the epithelioid cellular nodules in response to certain irritants or pathogenic agents might be another. Many attempts have been made to demonstrate such an abnormal reactivity, mainly with negative results.⁷ The "sarcoid reaction" as a response to quartz in normal subjects is essentially the same as in subjects with sarcoidosis, and in the case of most other extraneous substances the usual foreign body reaction is observed in sarcoidosis. The reaction to Kveim's antigen is an exception since definite but much delayed reactions are observed in 70% to 80% of the cases of sarcoidosis, with the production of a papule showing the epithelioid cellular structure of a sarcoid nodule. In normal subjects reactions are negligible or absent. This observation is not decisive, however, in proving an abnormal reactivity since it is still quite possible that some unidentified agent could be present in the lesions, which might excite an ordinary specific immunity reaction in subjects with the disease.

The impasse which has been reached in investigations along these lines has indicated clearly the need for a new approach to the problem. Recently some extensive epidemiological studies have been undertaken in a search for new leads. Michael et al.⁸ in 1950 reported a study based on 350 cases of sarcoidosis (proved by biopsy) observed in the military forces during

⁶ Sabin, F. R., Doan, C. A., and Forkner, C. E.: Studies on tuberculosis, J. Exper. Med. 52: Supp. 3, 1-152, 1930.

⁷ Refvem, O.: The pathogenesis of Boeck's disease (sarcoidosis), Acta med. Scandinav. (Suppl.) 294: 1-146, 1954.

⁸ Michael, M., Cole, R. M., Beeson, P. B., and Olson, B. J.: Sarcoidosis, Am. Rev. Tuberc. 62: 403-407, 1950.

World War II. The chief points brought out were the marked concentration of cases, based on the birth place, in the South Eastern states, the predominantly rural distribution, and the very high proportion of Negroes, about 20 times as many per 100,000 inductees as among the whites. Various speculative suggestions were advanced to explain these observations, but without adequate proof of any of them.

Gentry et al.⁹ in 1953 reported a further study of this group, with special reference to race, place of birth and induction, density of population and character of the soil. Again the high frequency ratio among inductees from the South Eastern states was found, nine times that of the North Eastern and Western sections of the country. This was due in substantial part to the large Negro population of this section and the greater susceptibility of this race to sarcoidosis. This could not explain the entire discrepancy, however, and some additional factor associated with the locality had to be assumed. As before, the frequency ratio was much higher in the sparsely populated rural areas. The only other factor recognized which they believed significant was the character of the soil. The highest incidence was in regions covered with what is technically known as Red Yellow Podzolic soil, in the Middle Coastal Plain region from Virginia to Texas, a light, sandy, strongly leached soil, in general scanty in organic and mineral plant nutrients. Aside from some slight content of beryllium in several samples, of doubtful significance, no characteristic of possible importance was recognized.

Cummings et al.¹⁰ carried out a similar epidemiologic study based on 1194 subjects diagnosed as sarcoidosis in 172 Veterans Administration hospitals between 1949 and 1954. They also found the hospitalization rate for Negro veterans much higher (12 times) than for whites. These cases were charted according to their place of birth, and in general their distribution confirmed the observations of Michael et al. as to the heavy concentration of cases in the South Eastern states. They found, however, a considerable number of cases in the North Central states and many also along the upper Atlantic Seaboard, including New England north through Massachusetts. This increased area no longer corresponds to that of the Podzolic soils postulated by Gentry et al. There was a correlation with nonarid areas in the United States and a good correlation with the distribution of forests in this country.

Following up this lead, Cummings and Hudgins¹¹ made a study of various forest products. They found that pine pollen (of two species)

⁹ Gentry, J. T., Nitowsky, H. M., and Michael, M. J.: Studies on the epidemiology of sarcoidosis in the United States: the relationship to soil areas and rural-urban residence, *J. Clin. Investigation* **34**: 1839-1856, 1955.

¹⁰ Cummings, M. M., Dumer, E., Schmidt, R. H., Jr., and Barnwell, J. B.: Concepts of epidemiology of sarcoidosis. Preliminary report of 1194 cases reviewed with special reference to geographic ecology, *Postgrad. Med.* **19**: 437-446, 1956.

¹¹ Cummings, M. M., and Hudgins, P. C.: Chemical constituents of pine pollen and their possible relationship to sarcoidosis, *Am. J. M. Sc.* **236**: 311-317, 1958.

takes the acid-fast Ziehl-Neelsen stain like tubercle bacilli. Pollen from two related genera (also gymnosperms) similarly gave a positive acid-fast stain but that from several unrelated trees (angiosperms) did not. They then undertook a chemical study of pine pollen to determine the presence of mycolic acid and of alpha epsilon diamino-pimelic acid (D.A.P.), which substances have been isolated from tubercle bacilli and (by Nethercott and Strawbridge¹²) from lungs and lymph nodes of cases of sarcoidosis but not from normal tissues. Mycolic acid was not demonstrated, but hydrolyzates of two species of pine pollen, of tubercle bacilli, and a solution of pure D.A.P. gave essentially similar paper chromatograms. These resembled those previously reported by others for D.A.P. They also obtained a "purified wax" both from pine pollen and from tubercle bacilli, which gave identical infrared spectra.

Injections of pine pollen suspended in paraffin oil into guinea pigs sensitized to tuberculin excited the production of nodules composed of epithelioid cells, like the "hard tubercle." Similar more localized lesions were obtained in normal guinea pigs. A phospholipid was extracted from the pollen which caused similar sarcoid-like lesions locally together with occasional giant cells in the spleen after intraperitoneal or subcutaneous injection. They did not, however, obtain dissemination of the nodular lesions by such injections.

These observations manifestly do not prove that pine (or other gymnosperm) pollen is the cause of sarcoidosis. They do give additional proof that many substances other than tubercle bacilli can stimulate the formation of epithelioid cellular granulomata and suggest that certain phospholipids play a large part in determining the characteristic features of the lesions. The geographical distribution of the pollen corresponds well enough with that of sarcoidosis to make it a possible suspect. More work along similarly independent lines is needed and may well be stimulated by these observations.

PAUL W. CLOUGH, M.D.

¹² Nethercott, S. E., and Strawbridge, W. G.: Identification of bacterial residues in sarcoid lesions, *Lancet* **22**: 1132, 1956.

REVIEWS

Financing Health Costs for the Aged. 239 pages; 14.5 × 22.5 cm. Office of the Special Assistant, Problems of the Aging, State Capitol, Albany, N. Y. 1957. Price, \$2.00.

This is a single volume report of a conference convened in 1956 by the Governor of New York State to help "older people finance the health care they require." For those who are concerned with the broad issues which fall within the general area of gerontology, this volume will prove a useful reference. For those who may be called upon to consider the medical care problems of the aged, particularly the economics of this subject, this volume will prove a valuable and rich source of pertinent data.

Brief addresses by five experts in the subject matter before the conference serve to outline the main issues which essentially are (1) the cost of medical care for non-institutionalized persons 65 years and over is 50 to 100 per cent higher than that of other age groups, (2) the increased cost of medical care in older ages is accompanied by a severe reduction in income associated with retirement, and (3) restrictive provisions of prepayment or insurance programs make it difficult for persons in older ages to continue coverage or to initiate insurance coverage.

Extensive tables are presented in support of the above generalizations. The data include (1) experience reported by the Social Security Administration which is responsible for the management of the Old Age and Survivors Insurance (O.A.S.I.) program, (2) the experience of several prepaid medical care and hospitalization services, and (3) the results of a nationwide survey of medical care costs financed by the Health Information Foundation.

Solutions for meeting the costs of the medical care of the aged are presented in clear concise form. A number of conference speakers refer to the possibility of including health benefits under the O.A.S.I., a matter which is the subject of proposed legislation before Congress at this time. In addition, feasible plans are advanced which would lead toward more comprehensive coverage of the costs of medical care of aged persons by existing voluntary health insurance systems.

This report is a necessary reference for commissions on aging, geriatrics committees, students of medical care economics and for administrators or members of the boards of voluntary health insurance programs.

MATTHEW TAYBACK, Sc.D.

The Pathology and Management of Portal Hypertension. By R. MILNES WALKER, M.S., F.R.C.S. 113 pages; 15 × 23.5 cm. The Williams & Wilkins Co., Baltimore. 1959. Price, \$8.00.

This small volume of 12 chapters is based on the author's personal experience in the surgical management of approximately 200 cases of portal hypertension during the past decade.

His concern is for the varix bleeder and to this end he succinctly describes the technical procedures designed to reduce portal pressure, or otherwise prevent varix rupture. Dr. Walker believes the main factors for success in operative treatment are the selection of patients and the appropriate operation. Therefore, stressed is the necessity for venography prior to any shunting procedure. Methods of venography are discussed and illustrated and the interpretations considered in detail with due regard for the pitfalls in diagnosis. Clinical and laboratory criteria for the selection

of suitable candidates are meager. Anatomy, physiology, and pathology are superficially covered.

An end-to-side portacaval anastomosis is the author's preference as it is more effective in lowering portal pressure and he considers it a less formidable procedure than splenorenal anastomosis which is resorted to only when the former is not possible. As less desirable measures, he describes such direct operations on the varices as portal-azygous disconnection, esophageal transection, ligation of varices, and esophagogastrectomy. Results of treatment compare favorably with published series of similar magnitude. Of special interest is the chapter devoted to portal hypertension in children. Instructive cases are well chosen to demonstrate the various etiologies of increased portal pressure and their attendant problems.

The view is expressed that, if varix hemorrhage persists or requires balloon tamponade for control, surgical intervention should be undertaken at once. No opinion is voiced on the advisability of a shunting procedure for patients with varices who have not bled. Double shunts are not considered. Perhaps the author is unable to confirm streamlining in the portal vein during venography because the specific gravity of contrast media is higher than that of blood.

The book will be valuable to both internists and surgeons concerned with bleeding esophageal varices.

J. E. K.

Pulmonary Circulation. By WRIGHT R. ADAMS, M.D., and ILZA VEITH, Ph.D. 316 pages; 18 × 26 cm. Grune & Stratton, New York. 1959. Price, \$4.50.

In March 1958, the Chicago Heart Association served as host to an international symposium on the Pulmonary Circulation. The program was broken into five half day sessions—one on the physiology and another on the pathology of the pulmonary circulation; one each on the pulmonary circulation in primary lung disease, in congenital heart disease, and in acquired heart disease.

During this time 30 papers were presented by internationally known men—20 from the U. S., 6 from Scandinavia and one each from Canada and Mexico. In this beautifully prepared volume the papers are reproduced along with the discussion that took place during the meeting in Chicago.

One paragraph from the preface describes the intent of the program very well: "No attempt was made to cover all phases of the subject or all diseases which involve the pulmonary circulation. Emphasis was always placed on new knowledge and its significance and interpretation. Obviously the subject matter did not lend itself to a division as clear-cut as is indicated by the titles of the sessions. However, the emphasis on the various categories was always maintained and the different sessions approached the same subject from distinctive points of view." This was the tone of the meeting proper; it is also the tone of this book.

Dr. Adams and Dr. Veith have done many a great service in preserving this meeting for more leisurely and thoughtful re-participation by those who heard the papers. They also deserve great thanks from the much larger number of interested persons who did not attend.

B. W. A.

Pediatric Methods and Standards. 3rd Ed. Edited by FRED H. HARVIE, M.D., Associate Professor of Clinical Pediatrics, School of Medicine, University of Pennsylvania. 324 pages; 12 × 20.5 cm. (loose-leaf). Lea & Febiger, Philadelphia. 1958. Price, \$4.50.

This book is a manual for a pediatric house-staff, produced by more than eight years of accumulation and condensation. A very large amount of information is

available in these 324 pages. The size of this book illustrates the complexity of modern medicine; though its contents are selected and condensed as far as practical, and though it concerns only a small aspect of one specialty, it is still too large for the pocket. Among the subjects discussed are growth and development, laboratory tests and their results, drugs and dosages, periods of quarantine, and weights and measures. Data in these and other fields are easily accessible, and references are given when necessary. Although the data are necessarily dry and technical, the author's concern for the whole patient is evident in his sections on history-taking, tracheotomy, antibacterial therapy, and elsewhere. This is a good manual.

We would have preferred a shorter presentation of growth and a longer, illustrated presentation of electrocardiography, and in the description of the physical examination some special emphasis on gait, speech, hearing, and sight, as these are neglected so often.

G. S. C.

Therapeutic Exercise. Volume III of Physical Medicine Library. Edited by SIDNEY LICHT, M.D. 893 pages; 23.5 × 16 cm. Elizabeth Licht, Publisher, New Haven, Connecticut. 1958. Price, \$16.00.

As indicated by the editor, this is the most complete book ever published on the subject of therapeutic exercise. There are 35 chapters and two appendices written by 37 different authors. The book is arranged primarily in two parts, the first half being devoted to the basic anatomy, physiology and principles of therapeutic exercise and the second half to its application to various diseases.

The chapter on manual muscle examination is very well written and could be useful to almost every physician. The 10 chapters on exercises used in the treatment of disease are comprehensive and include the common neurological, orthopedic and medical conditions responding to such treatment. In addition there are chapters devoted to exercise in mental disease, obstetrics, ophthalmology and in healthy persons. An interesting chapter is devoted to the history of exercise and one also to the controversial subject of proprioceptive facilitation.

Appendix I discusses the newer concept of isometric exercise for increasing muscle strength as compared to the traditional isotonic method. Appendix II defines many of the terms used and also briefly describes other miscellaneous subjects related to exercise not adequately covered in the text.

This book, because of the scope of its subject, could not possibly be all inclusive but it offers the most complete and readily available information to date. It should be a useful reference book to interested physicians, particularly physiatrists, orthopedists and neurologists, and to physical therapists.

PAUL F. RICHARDSON, M.D.

Streptomycin and Dihydrostreptomycin. Antibiotics Monographs No. 10. (Under the Editorial Direction of HENRY WELCH, Ph.D., and FÉLIX MARTÍ-IBÁÑEZ, M.D.) By LOUIS WEINSTEIN, Ph.D., M.D., Professor of Medicine, Tufts University School of Medicine, etc.; and N. JOEL EHRENKRANZ, M.D., Assistant Professor of Medicine, University of Miami School of Medicine, etc.; foreword by CHESTER S. KEEFER, M.D. 116 pages; 23.5 × 16 cm. Medical Encyclopedia, Inc., New York. Price, \$4.00.

This is the tenth in the "Antibiotics Monographs" series published by Medical Encyclopedia, Inc. It is concerned with the presentation of a summary of available knowledge of streptomycin, exclusive of the field of tuberculosis, which aspect is treated in another volume of the series.

The authors present in detail the appropriate basic pharmacologic and microbiologic aspects of SM and DHSM, then consider the clinical situations in which SM may be useful, or contrariwise, of limited usefulness. The material is clearly presented, and extensively documented in a comprehensive bibliography.

The book serves a very useful purpose in providing in one small volume a succinct but thorough presentation of available knowledge of the streptomycins.

PATRICK B. STOREY, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Aportes a la Terapéutica de Algunas Enfermedades. By JUAN RAMON URIZ. 197 pages; 19.5 × 14 cm. (paper-bound). 1959. Ministerio de Comunicaciones, Buenos Aires, Argentina.

The Biochemistry of Clinical Medicine. 2nd Ed. By WILLIAM S. HOFFMAN, Ph.D., M.D., F.A.C.P., Professorial Lecturer in Medicine, University of Illinois College of Medicine, etc. 734 pages; 25 × 16.5 cm. 1959. The Year Book Publishers, Inc., Chicago. Price, \$12.00.

Biosynthesis of Terpenes and Sterols. Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and MAEVE O'CONNOR, B.A. 311 pages; 21 × 14 cm. 1959. Little, Brown and Company, Boston. Price, \$8.75.

A Doctor Discusses Menopause. By G. LOMBARD KELLY, A.B., B.S. Med., M.D. 90 pages; 18 × 14 cm. (paper-bound). 1959. The Budlong Press, Chicago. Price, \$1.50.

Expert Committee on Auxiliary Dental Personnel: Report. World Health Organization Technical Report Series No. 163. 32 pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

The Foreign Student and Post-graduate Public Health Courses: Sixth Report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel. World Health Organization Technical Report Series No. 159. 23 pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Glaucoma: Transactions of the Third Conference, January 8, 9, and 10, 1958, Princeton, N. J. Edited by FRANK W. NEWELL, M.D., Department of Surgery (Ophthalmology), The University of Chicago, Chicago, Illinois. 272 pages; 24 × 16 cm. 1959. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$5.25.

Headache: Diagnosis and Treatment. By ARNOLD P. FRIEDMAN, M.D., Associate Clinical Professor of Neurology, Columbia University, etc.; and H. HOUSTON MERRITT, M.D., Professor of Neurology, Columbia University, etc. 401 pages; 23.5 × 15.5 cm. 1959. F. A. Davis Company, Philadelphia. Price, \$8.00.

Immunity and Resistance to Infection in Early Infancy: Report of the Twenty-ninth Ross Pediatric Research Conference. Editor: SAMUEL J. FOMON, M.D., College of Medicine, State University of Iowa; Associate Editor: JAMES E. JEFFRIES,

Ross Laboratories. 95 pages; 23 × 15 cm. (paper-bound). 1959. Ross Laboratories, Columbus, Ohio. Available on request.

The Medical Secretary in a Medical, Hospital, or Dental Office. By KENNETH B. COFFIN, Professor of Business, Head of the Department of Secretarial Administration, San Jose State College, California; and R. FORREST COLWELL, Colwell Publishing Company, Champaign, Illinois. 391 pages; 21.5 × 14.5 cm. 1959. The Macmillan Company, New York. Price, \$5.95.

Les Médicaments du Système Nerveux Cérébro-spinal: Pharmacologie et applications anesthésiologiques, neuro-psychiatriques et thérapeutiques. Publié sous la direction du PROFESSEUR F. MERCIER. 573 pages; 24.5 × 16.5 cm. (paper-bound). 1959. Masson et Cie, Editeurs, Libraires de l'Académie de Médecine, Paris. Price, 5800 fr.

Medicina Interna de Urgencia y de Cuadros Agudos. 2nd Ed. By EGIDIO S. MAZZEI and M. LETICIA DIAZ SOTO DE MAZZEI. 959 pages; 23.5 × 16 cm. (paper-bound). 1958. Lopez & Etchegoyen, S.R.L., Buenos Aires. Price, m\$n 650.

Now or Never: The Promise of the Middle Years. By SMILEY BLANTON, M.D., with ARTHUR GORDON. 273 pages; 23.5 × 15.5 cm. 1959. Prentice-Hall, Inc., Englewood Cliffs, N. J. Price, \$4.95.

Parasitology (Protozoology and Helminthology) in Relation to Clinical Medicine. 2nd Ed. By K. D. CHATTERJEE, M.D. (Calcutta), Associate Professor of Medicine, R. G. Kar Medical College and Physician, R. G. Kar Medical College Hospitals, Belgachia, Calcutta. 188 pages; 25.5 × 17.5 cm. 1959. Published by the author, 6, Amrita Banerjee Road, Kalighat, Calcutta 26, India. Price, Rs17.50.

Pathology. 2nd Ed. By PETER A. HERBUT, M.D., Professor of Pathology, Jefferson Medical College and Director of Clinical Laboratories, Jefferson Medical College Hospital, Philadelphia, Pennsylvania. 1,516 pages; 26 × 18.5 cm. 1959. Lea & Febiger, Philadelphia. Price, \$18.50.

Persons Injured by Class of Accident, United States, July 1957-June 1958. Statistics on the Number of Persons Injured, Class of Accident, and Days of Disability Due to Injuries by Age, Sex, Residence, Family Income, and Major Activity. Based on Data Collected in Household Interviews During the Period, July 1957-June 1958. Health Statistics from the U. S. National Health Survey, Public Health Service Publication No. 584-B8. 62 pages; 26 × 20 cm. (paper-bound). 1959. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 40¢.

Précis de Thérapeutique et de Pharmacologie. Supplément (1959) à la Neuvième Édition. Par RENÉ HAZARD. 138 pages; 19.5 × 13.5 cm. (paper-bound). 1959. Masson et Cie, Editeurs, Libraires de l'Académie de Médecine, Paris. Price, 320 fr.

Psychiatric Consultation for Nonpsychiatric Professional Workers: A Concept of Group Consultation Developed from a Training Program for Nurses. Public Health Monograph No. 53. By BEULAH PARKER, M.D. 23 pages; 26 × 20 cm. 1958. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 25¢.

Public Health Nursing: Fourth Report of the Expert Committee on Nursing. World Health Organization Technical Report Series No. 167. 31 pages; 24 × 16 cm.

(paper-bound). 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Radiation Biology and Cancer: A Collection of Papers Presented at the Twelfth Annual Symposium on Fundamental Cancer Research, 1958. 493 pages; 24 × 16 cm. 1959. Published for The University of Texas M. D. Anderson Hospital and Tumor Institute by the University of Texas Press, Austin, Texas. Price, \$8.50.

Structure et Ultra-structure Rénale. Aspects Normaux et Pathologiques—Microscopie Électronique. La Ponction-Biopsie du Rein. Par JEAN PUTOIS, Chef de Clinique Médicale; avec la collaboration de Y. DENARD, G. MOREAU, J.-M. SUC et C. REGNIER. 170 pages; 24 × 15.5 cm. (paper-bound). 1959. Librairie Arnette, Paris. Price, 2.500 fr.

A Text on Systemic Pathology. Vol. II. Edited by OTTO SAPHIR, M.D., Director, Department of Pathology, Michael Reese Hospital, Chicago, Illinois, etc. 1,950 pages; 28 × 20.5 cm. 1959. Grune & Stratton, Inc., New York. Price, \$38.00.

Therapeutic Electricity and Ultraviolet Radiation. Vol. IV of *Physical Medicine Library.* Edited by SIDNEY LICHT, M.D., Honorary Member, British Association of Physical Medicine, etc. 373 pages; 23.5 × 15.5 cm. 1959. Elizabeth Licht, Publisher, New Haven, Connecticut. Price, \$10.00.

Total Surgical Management. Modern Surgical Monographs 1. (Editor in Chief: I. S. RAVDIN, M.D.; Consulting Editor: RICHARD H. ORR, M.D.) By JAMES D. HARDY, M.S., M.D., F.A.C.S., Professor and Chairman, Department of Surgery, University of Mississippi Medical Center, Jackson, Mississippi. 292 pages; 23.5 × 15.5 cm. 1959. Grune & Stratton, Inc., New York. Price, \$9.50.

Tuberculosis and Other Communicable Diseases. By J. ARTHUR MYERS, M.D., Professor of Internal Medicine and Public Health, Medical, Public Health and Graduate Schools, University of Minnesota; with an introduction by IRVINE MCQUARRIE, A.B., Ph.D., M.D. 499 pages; 23.5 × 16 cm. 1959. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$14.50.

Tuberculosis Medical Research: National Tuberculosis Association, 1904-1955. Historical Series No. 9. By VIRGINIA CAMERON, Formerly Medical Research Secretary, National Tuberculosis Association; and ESMOND R. LONG, M.D., Formerly Director of Medical Research, National Tuberculosis Association. 325 pages; 23.5 × 16 cm. 1959. National Tuberculosis Association, New York. Price, \$5.00.

Your Mind Can Make You Sick or Well. By CURT S. WACHTEL, M.D. 244 pages; 23.5 × 16 cm. 1959. Prentice-Hall, Inc., Englewood Cliffs, N. J. Price, \$4.95.

COLLEGE NEWS NOTES

ABSTRACT OF THE PRESIDENTIAL ADDRESS OF ELBERT L. PERSONS, M.D., TO THE THIRD ANNUAL MEETING OF THE AMERICAN SOCIETY OF INTERNAL MEDICINE, CHICAGO, APRIL 19, 1959

It is true that the organization of the American Society of Internal Medicine served as a stimulus for the organization of many of our component Societies. However, our growth within 3 years to 44 Societies with 5,400 members has occurred because of a clear recognition of the function of the Internist in the care of the patient in his own local area and of the need that this function be recognized if patients are to continue to receive good medical care.

As of February 1959, I was able to report that two-thirds of our membership has been certified by the American Board of Internal Medicine or are members of the A.C.P. We had attracted Board Certified Internists who had not become members of the American College of Physicians but had joined a State Society of Internal Medicine. We have incomplete information on approximately eleven hundred members, many of whom must have secured Board Certification or membership in the American College of Physicians since our rosters were submitted.

I can report that our relationships with other organizations at the national level have been entirely pleasant and productive. The coöperation of the American College of Physicians has continued, and members of our Society have been offered the same privileges which members of the College enjoy as to hotel reservations to continue through the College meeting. Non-members of the College will be sponsored as guests if they wish to register for the annual session. The American Medical Association gave us invaluable assistance in the search for a competent and experienced Executive Director and has coöperated in the development of the program you will hear today. We are honored by the fact that Dr. Louis Orr, President-Elect of the American Medical Association will be our first speaker on the afternoon session. The Health Insurance Council and the National Association of Blue Shield sent speakers to the meeting of our Committee on Medical Services in New Orleans last November, and their comments and advice were very helpful to us. General Robinson, formerly in charge of the Medicare Program, is on our afternoon program by courtesy of the Metropolitan Life Insurance Company.

All of the leaders of our component societies whom I have met seem to be outstanding Internists, so well established as specialists that they are obviously working to maintain and promote the status of the specialist in Internal Medicine without prospect of personal gain. In many States these leaders have come to the conclusion that the services characteristic of a specialist in Internal Medicine must be recognized in the community where they are performed, and that it is not possible for any medical society to dictate who is actually to perform these services. These leaders have been able to produce rosters of Internists in each State which could be accepted as representative of those Specialists who are actually in the practice of Internal Medicine.



HOWARD P. LEWIS, B.S., M.D., F.A.C.P.
Portland, Ore.
President, American College of Physicians

THE PRESIDENT

HOWARD P. LEWIS, 3181 S. W. Sam Jackson Park Road, Portland 1, Oregon. Born, February 18, 1902, at San Francisco, California. B.S., Engineering, Oregon State College, 1924; M.D., University of Oregon Medical School, 1930. Internship and Residency served at the University of Oregon Medical School Hospitals and Clinics; Assistant in Anatomy, 1926-29, Instructor in Anatomy, 1929-30, Instructor in Medicine, 1929-30, Clinical Instructor in Medicine, 1932-36, Clinical Associate in Medicine, 1936-38, Assistant Clinical Professor of Medicine, 1938-42, Associate Professor of Medicine, 1946-47, Professor of Medicine and Head of Department, 1947 to date, University of Oregon Medical School; served in the U. S. Army Medical Department from 1942 to 1946, rising from Major to Colonel; Assistant Chief of Medical Service, Halloran General Hospital, Staten Island, N. Y., 1942-43; Chief of Medical Service, Rhoads General Hospital, Utica, N. Y., 1943-45; Consultant in Medicine, Second Service Command, Governor's Island, N. Y., 1945-46.

Past Chairman, Section on Internal Medicine, American Medical Association; Past President, North Pacific Society of Internal Medicine; Chairman, American Board of Internal Medicine; Member, Advisory Council of the National Heart Institute of the U. S. Public Health Service; Member, Pacific Interurban Clinical Club, American Heart Association, American Federation for Clinical Research, Western Society for Clinical Research, Western Association of Physicians, American Clinical and Climatological Association, Association of American Physicians, Society of Medical Consultants to the Armed Forces, American Association for the Advancement of Science, Sigma Xi, Alpha Omega Alpha. Editor, Modern Concepts of Cardiovascular Disease, American Heart Association since 1956.

The American College of Physicians—Fellow, 1942; Governor for Oregon, 1948-51; Third Vice President, 1951-52; Regent, 1952-58; President-Elect, 1958-59; installed as President, April 23, 1959; Member of many committees, past and present.



CHESTER S. KEEFER, B.S., M.S., D.Sc.(Hon.), M.D., F.A.C.P.

Boston, Mass.

President-Elect, American College of Physicians

THE PRESIDENT-ELECT

CHESTER SCOTT KEEFER, 65 E. Newton St., Boston 18, Mass. Born May 3, 1897, Altoona, Pa. B.S., 1918, M.S., 1922, D.Sc. (Hon.), 1944, Bucknell University; M.D., 1922, The Johns Hopkins University School of Medicine; D.Sc. (Hon.), 1944, Boston University School of Medicine. Resident House Officer, 1922-23, Resident Physician, 1923-26, Johns Hopkins Hospital, Baltimore, Md.; Resident Physician, Albert Merritt Billings Hospital, Chicago, Ill., 1926-28. Assistant in Medicine, 1923-25, Instructor in Medicine, 1925-26, The Johns Hopkins University School of Medicine. Associate Professor of Medicine, 1928-30, Peiping Union Medical College, Peiping, China. Assistant Professor of Medicine, 1930-36, Associate Professor of Medicine, 1936-40; Harvard Medical School. Wade Professor of Medicine since 1940 and Director since 1955, Boston University School of Medicine. Associate Physician, Thorndike Memorial Laboratory, 1930-40, and Director, 2nd and 4th Medical Services and Chief, 4th Medical Service, 1939-40, Boston City Hospital; Physician-in-Chief and Director, Robert Dawson Evans Memorial Department of Clinical Research and Preventive Medicine since 1940, Massachusetts Memorial Hospitals. Executive Committee, Division of Medical Science, National Research Council since 1956; Chairman, Committee on Research, American Medical Association; Special Assistant to the Secretary of Health, Education and Welfare, Washington, D. C., 1953-55. Medical Administrative Officer, Committee on Medical Research, office of Scientific Research and Development, 1944-46. Director, Commission on Hemolytic Streptococcal Infections, Army Epidemiology Board, 1942-43. Member, American Society for Clinical Investigation; Association of American Physicians; Councillor, American Clinical and Climatological Association; Society for Experimental Biology and Medicine; American Academy of Arts and Sciences; American Philosophical Society; Interurban Clinical Club; Phi Gamma Delta; Phi Chi; Alpha Omega Alpha; Diplomate, American Board of Internal Medicine. Decorated, Medal of Merit (U. S.); His Majesty's Medal (Great Britain).

The American College of Physicians—Follow, 1931; Governor for Massachusetts, 1944-53; General Chairman, 31st Annual Session, Boston, Mass., 1950; Regent, 1953-59; American College of Physicians Representative to Division of Medical Science, National Research Council, 1956-59; Chairman, Committee on Fellowships and Scholarships, 1956-59, President-Elect, 1959-60. Member of many committees, past and present.

BOOKS DONATED TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College gratefully acknowledges receipt of the following books from members of the College to the Memorial Library of Publications by Members of the College:

Walter C. Alvarez, M.D., F.A.C.P., Chicago, Ill., PRACTICAL LEADS TO PUZZLING DIAGNOSES: NEUROSES THAT RUN THROUGH FAMILIES, published by J. B. Lippincott Co., Philadelphia, Pa., 1958, 490 pages.

Robert S. Wallerstein, M.D., F.A.C.P., Topeka, Kans., THE TEACHING AND LEARNING OF PSYCHOTHERAPY, published by Basic Books, Inc., New York, N. Y., 1958, 334 pages.

Louis Weinstein, M.D., F.A.C.P., Boston, Mass., STREPTOMYCIN AND DIHYDROSTREPTOMYCIN, published by Medical Encyclopedia, Inc., New York, N. Y., 1958, 116 pages.

Henry A. Zimmerman, M.D., F.A.C.P., Cleveland, Ohio, INTRAVASCULAR CATHETERIZATION, published by Charles C Thomas, Springfield, Ill., 1959, 782 pages.

NEW LIFE MEMBERS

The College acknowledges with pleasure the following new Life Members:

- Dr. Joseph Bank, Phoenix, Ariz.
 - Dr. Edward R. Evans, Pasadena, Calif.
 - Dr. Henry J. Lehnhoff, Jr., Omaha, Nebr.
 - Dr. Miriam Lincoln, Mercer Island, Wash.
 - Dr. Herbert J. Rinkel, Kansas City, Mo.
 - Dr. Frederick T. Schnatz, Buffalo, N. Y.
 - Dr. R. S. Ylvisaker, Minneapolis, Minn.
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**CONSTITUTION AND BY-LAWS OF THE AMERICAN COLLEGE OF PHYSICIANS
EXTENSIVELY REVISED**

At the Annual Business Meeting of the College at Chicago on April 23, 1959, the Constitution and By-Laws of the College were extensively amended. The proposed amendments appeared in the February, 1959, Issue of the ANNALS OF INTERNAL MEDICINE, but in two particular instances, those proposals were further changed, to wit:

BY-LAWS, Article II, Section 2, "the elected Members of the Board of Regents shall each serve for a term of three years, and for not more than *two* consecutive terms, exclusive of any unexpired fraction of a term previously served."

BY-LAWS, Article III, Section 1, Executive Committee. "Membership: The Board of Regents shall elect annually four of its members; these, together with the President, President-Elect, Secretary-General, Treasurer, Chairman of the Board of Governors, and Chairman of the Committee on Finance and Budgets, shall constitute an Executive Committee. Members of the Executive Committee shall be eligible for reëlection."

Other than for the above revisions, the proposed amendments were adopted exactly as submitted to the Fellows and Masters in the News Notes Section of the February Issue of this Journal.

One of the most far-reaching changes in the By-Laws relates to the readmission of an Associate whose term expired because of inability to fulfill the requirements for advancement to Fellowship. Heretofore, such an Associate, to reenter the College, was required to be re-proposed for Associateship, and, if reelected, he was required to serve at least a minimal period of three years before he could advance to Fellowship. Under the amended By-Laws, Article VIII, Section 5, last paragraph, it is provided "if Associateship has been terminated . . . but the individual specifically becomes able to fulfill all requirements for advancement to Fellowship to the complete satisfaction of the Committee on Credentials, he may be re-proposed to the Committee on Credentials, which body may recommend to the Board of Regents his reinstatement as an Associate and his immediate advancement to Fellowship."

REPUBLICATION OF THE AMERICAN COLLEGE OF PHYSICIANS DIRECTORY

The Board of Regents of the College has established a rule that the Directory shall be revised and republished every three years, with an annual Supplement during each intervening year.

The Executive Office of the College is now engaged in the republication of the Directory and plans to bring out the new edition before the end of 1959. Each member of the College is urged to return immediately and without delay the questionnaire recently distributed, in order that his biographical data shall be brought entirely up to date. A directory that is not completely correct and the biographical data of its members not fully up to date is of questionable value and lacks authority. The Officers of the College, therefore, appeal for full and prompt coöperation on the part of each and every Member.

Life Members will receive a copy of the new Directory without charge. Other members may subscribe at the pre-publication price of \$9.00, postpaid, which represents the basic cost. The post-publication price will be \$12.00. The new Directory will contain the names, specialties and biographical data of all living members, 10,247, and will consist of a bound volume of an estimated 1,400 pages.

AMERICAN BOARD OF RADIOLoGY

Tulley
The American Board of Radiology will conduct a special examination in Nuclear Medicine for diplomates in Radiology or Therapeutic Radiology on December 5, 1959. Applications for this examination must be submitted by August 1, 1959. Write to H. Dabney Kerr, M.D., The American Board of Radiology, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF INTERNAL MEDICINE

Written examinations conducted by the American Board of Internal Medicine will be held on October 17, 1960. The candidates must file applications on or before May 1, 1960. For information write William A. Werrell, M.D., Executive-Secretary-Treasurer, American Board of Internal Medicine, One W. Main St., Madison 3, Wis.

COMING REGIONAL MEETINGS

| <u>State(s)</u> | <u>City</u> | <u>Date</u> | <u>Governor(s)</u> | <u>Official Guest(s)</u> |
|--|------------------------------------|---|---|-------------------------------|
| Oklahoma-Arkansas | Tulsa, Okla. | September 19, 1959 | Bert F. Keltz, M.D., F.A.C.P. John N. Compton, M.D., F.A.C.P. | |
| Mid-West (Ill., Ind., Iowa, Minn., Wis.) Western New York | Indianapolis, Ind. Buffalo | September 26, 1959 October 9, 1959 | Kenneth G. Kohlstaedt, M.D., F.A.C.P. John H. Talbott, M.D., F.A.C.P. | |
| New England States and Canada (Conn., Maine, Mass., N.H., R.I., Vt., Quebec, Newfoundland, Nova Scotia, New Brunswick, P.E.I.) | Providence, R. I. | October 23-24, 1959 | Marshall N. Fulton, M.D., F.A.C.P. | |
| Southeastern States (Ala., Fla., Ga., Miss., S. C., Cuba) | Columbia, S. C. | October 30-31, 1959 | Orlando B. Mayer, M.D., F.A.C.P. | Howard P. Lewis, President |
| Maryland-District of Columbia | Baltimore | November 7, 1959 | R. Carmichael Tilghman, M.D., F.A.C.P. Theodore J. Abernethy, M.D., F.A.C.P. | Howard P. Lewis, President |
| New Jersey | | November 11, 1959 | Roy W. Black, M.D., F.A.C.P. | Howard P. Lewis, President |
| North Carolina | Chapel Hill | December 3, 1959 | Robert L. McMillan, M.D., F.A.C.P. | |
| Ohio-Western Pennsylvania | | January 28-29, 1960 | Carlton Ernstene, M.D., F.A.C.P. | |
| Southern California Kansas Nebraska | Coronado Kansas City Lincoln | February 6-7, 1960 March 4, 1960 March 19, 1960 | Frank J. Gregg, M.D., F.A.C.P. George C. Griffith, M.D., F.A.C.P. Fred J. McEwen, M.D., F.A.C.P. Edmond M. Walsh, M.D., F.A.C.P. | |

LIFE INSURANCE MEDICAL RESEARCH FELLOWSHIPS AND GRANTS

The Life Insurance Medical Research Fund is now receiving applications for two types of awards to be available July 1, 1960, as follows: (1) Until October 15, 1959, for postdoctoral research fellowships, candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on fundamental problems, especially those related to cardiovascular function or disease. Minimum stipend \$4,500, with allowances for dependents and necessary travel; (2) Until November 1, 1959, for grants to institutions in aid of research on cardiovascular problems, support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems, as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 E. 46th St., New York 17, N. Y.

COURSE IN POSTGRADUATE GASTROENTEROLOGY

The American College of Gastroenterology announces that its Annual Course in Postgraduate Gastroenterology will be given at the Biltmore in Los Angeles, Calif., on September 24-26, 1959. The faculty for the course will be drawn from the medical schools in and around Los Angeles. The subject matter, to be covered from a medical as well as surgical viewpoint, will be essentially the advances in diagnosis and treatment of gastrointestinal diseases and a comprehensive discussion of diseases of the mouth, esophagus, stomach, pancreas, spleen, liver and gallbladder, colon and rectum. There will be a clinical session at the College of Medical Evangelists and this year, in addition to individual papers, there will be several panel discussions of interest. For further information and enrollment, write to the American College of Gastroenterology, 33 W. 60th St., New York 23, N. Y.

ARTHRITIS AND RHEUMATISM FOUNDATION ANNOUNCES FELLOWSHIP PROGRAM

The Arthritis and Rheumatism Foundation offers predoctoral, postdoctoral and senior investigatorship awards in the fundamental sciences related to arthritis for work beginning July 1, 1960. Deadline for applications is October 31, 1959. These awards are intended as fellowships to advance the training of young men and women of promise for an investigative or teaching career. They are not in the nature of a grant-in-aid in support of a research project.

The program provides for three awards: (1) Predoctoral Fellowships are limited to students who hold a bachelor's degree. Each applicant studying for an advanced degree must be acceptable to the individual under whom the work will be done. These Fellowships are tenable for one year, with prospect of renewal. Stipends range from \$1,500 to \$3,000 per year, depending upon the family responsibilities of the Fellow. (2) Postdoctoral Fellowships are limited to applicants with the degree of Doctor of Medicine, Doctor of Philosophy—or their equivalent. These Fellowships are tenable for one year, with prospect of renewal. Stipends range from \$4,000 to \$6,000 per year, depending upon the family responsibilities of the Fellow. (3) Senior Investigator Awards are made to candidates holding or eligible for a "faculty rank" such as Instructor or Assistant Professor (or equivalent) and who are sponsored by their institution. Stipends are from \$6,000 to \$10,000 per year and are tenable for five years.

A sum of \$500 will be paid to cover the laboratory expenses of each postdoctoral fellow and senior investigator. An equal sum will be paid to either cover the tuition expenses or laboratory expenses of each predoctoral fellow.

For further information and application forms, address the Medical Director, Arthritis and Rheumatism Foundation, 10 Columbus Circle, New York 19, N. Y.

POSTGRADUATE COURSE IN OCCUPATIONAL SKIN PROBLEMS

The Institute of Industrial Health of the University of Cincinnati announces that the Fourth Biennial Course of Instruction in Occupational Skin Problems will be held during the week of October 26-30, 1959. It will be presented by the Department of Preventive Medicine and Industrial Health, University of Cincinnati College of Medicine, in collaboration with the Occupational Health Program of the United States Public Health Service, and the Department of Dermatology of the University. The objective of this course is to give physicians a greater understanding of cutaneous problems of occupational origin.

The program will be divided into daily sessions, consisting of morning lectures and clinical demonstrations, afternoon field instruction in industrial plants, and evening panel discussions. The didactic presentations will include a review of the anatomy, physiology and chemistry of the skin. Detailed consideration will be given to the etiology, diagnostic evaluation and treatment of occupational dermatoses, as well as specific measures for prevention and control of these problems. Current concepts regarding cutaneous cancer, allergic reactions and medicolegal problems will be discussed. Early application is advised since attendance will be limited. For information, write to the Secretary, Institute of Industrial Health, The Kettering Laboratory, Eden and Bethesda Aves., Cincinnati 19, Ohio.

COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION

A Course in Electrocardiographic Interpretation for graduate physicians will be given at the Michael Reese Hospital, Chicago, Ill., by Louis N. Katz, M.D., F.A.C.P., Alfred Pick, M.D., (respectively Director and Associate Director of the Cardiovascular Department) and Associates. The class will meet daily from 9:00 a.m. to 5:00 p.m., August 17-29, 1959. For further information, write Miss Beverley Petzold, Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

AMERICAN HEART ASSOCIATION OFFERS RESEARCH SUPPORT

Applications are now being accepted by the American Heart Association for support of research to be conducted during the fiscal year beginning July 1, 1960. September 15, 1959, is the deadline for applying for Research Fellowships and Established Investigatorships. Applications for Grants-in-Aid must be made by November 1, 1959.

Public contributions to the annual Heart Fund campaign provide the funds for Association-supported research. Support is given not only to studies with a direct bearing on problems of cardiovascular medicine, but also to basic research in a wide range of scientific disciplines. The Association recently announced its national awards for the 1959-60 fiscal year, representing an allocation of approximately \$3,300,000.

Following are brief accounts of the categories in which applications may be made: *Established Investigatorships*: Awarded for periods of up to five years, subject to annual review, in amounts ranging from \$6,500 to \$8,500 yearly plus dependency allowances, to scientists of proved ability who have developed in their research careers to the point where they are independent investigators. In addition, a grant of \$500 is made to the investigator's department. Applicants for Established In-

vestigatorships may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships. *Advanced Research Fellowships:* Awarded for periods of one or two years to postdoctoral applicants who have had some research training and experience, but who are not clearly qualified to conduct their own independent research. During the second year of tenure they will be permitted to spend up to 25 per cent of their time in professional and scientific activities not strictly of a research nature, provided that these will contribute to their professional development and do not involve services for a fee. These stipends range from \$4,600 to \$6,500 annually. Additionally, a grant of \$500 is made to the investigator's department, as in the case of Established Investigators. *Research Fellowships:* A limited number of awards are available to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from \$3,800 to \$5,700. *Grants-in-Aid:* Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

Further information and application forms may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 E. 23rd St., New York 10, N. Y.

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ANNOUNCES
NEW PROFESSIONAL CATEGORY

A new category of professional personnel in fields related to health and medicine has been established in the Commissioned Corps of the U. S. Public Health Service, Surgeon General Leroy E. Burney, F.A.C.P., Washington, D. C., announced recently. It is known as the Health Services category and brings to 11 the number of professional groups now comprising the Commissioned Corps.

The Health Services category includes Commissioned Officers who are health educators, nutritionists, medical record librarians, hospital administrators, medical social workers, and personnel in related health fields.

The Health Services category was established to provide a more precise classification for Public Health Service Commissioned Officers in the health-related professions. Officers being assigned to the new category were formerly assigned to a general category known as sanitarians. The Sanitarian category is being retained in the Commissioned Corps to provide a classification for professional sanitarians.

No change in entrance requirements, pay and allowances, grades, or promotion policies affecting officers of the Commissioned Corps is involved in the creation of the new category.

In addition to the Health Services and Sanitarian categories, the Corps includes officers in the Medical, Dental, Nurse, Scientist, Veterinarian, Pharmacist, Sanitary Engineer, Therapist and Dietitian categories.

DR. LOUIS H. BAUER HONORED

The Headquarters Secretariat of The World Medical Association recently announced that it had received a portrait in oil of Dr. Louis H. Bauer, F.A.C.P., New York, N. Y., its Secretary General since 1948. Bena Frank Mayer, a New York artist, was commissioned by the Board of Directors of the United States Committee, Inc., of the World Medical Association to do the portrait.

Dr. Austin Smith, Chairman of the Board of Directors and President of the Pharmaceutical Manufacturers Association presented the painting, suitably framed for display at the Secretariat, at the conclusion of the 12th Annual Meeting of the Board of Directors of the United States Committee, Inc.

Dr. Louis H. Bauer has served as Secretary-Treasurer of the Board of Directors of the United States Committee, Inc., since its organization in February, 1948.

TRAINING PROGRAM IN THE FIELD OF HUMAN GENETICS

Dr. George E. Armstrong, F.A.C.P., Vice Chancellor for Medical Affairs, New York University, New York, N. Y., recently announced the New York University-Bellevue Medical Center had received a \$200,000 grant from the United States Public Health Service which will be used to develop a training program in the field of human genetics with special emphasis on cardiovascular research. The project will be under the direction of Dr. Charles F. Wilkinson, Jr., F.A.C.P., Professor and Chairman of the Department of Medicine of the Post-Graduate Medical School and Director of the 4th Medical (New York University) Division, Bellevue Hospital.

The program will offer three years of intensive basic training in human genetics to physicians who desire to continue in full-time research and academic medicine. Part of the training will provide experience in a counselling clinic which will draw from the personnel who form the corps of instructors. This group of instructors will represent those most interested in carrier individuals and their detection, and those who are working on the early detection of potential disease caused by inherited traits which are slow to manifest themselves clinically. The predominance of clinical research will be in the field of cardiovascular disease because of its overwhelming importance at the present time.

PAN AMERICAN MEDICAL ASSOCIATION

The next Pan American Medical Association Congress will meet in Mexico City, May 2-11, 1960, it was announced recently by Joseph J. Eller, M.D., Director-General of the Pan American Medical Association. Early indications point to the largest and most significant Congress in the 34-year-old organization's history. The scientific program, through its 48 different medical sections, will include all branches of medicine and surgery, dentistry, hospital administration, and medical education.

New sections added since the last Pan American Medical Association Congress include Space Medicine, Hematology, and Cancer Cytology. There will be many special panels, including Pharmacology and New Drugs, Mental Diseases, Nutrition, Relationship of Dentistry to Medicine, Cancer Research, Sudden Deaths, and Medical Press Relations, and others.

The Congress will also have scientific and commercial exhibits, medical motion pictures, and closed circuit television demonstrations of new techniques. Tours will be arranged to the various institutions by the Mexican Chapter of PAMA.

For information, write Joseph J. Eller, M.D., Director-General of the Pan American Medical Association, 745 Fifth Ave., New York 22, N. Y.

50TH ANNIVERSARY OF "THE ORANGE CROSS" INTERNATIONAL JUBILEE CONFERENCE, 1959

The 50th Anniversary of "The Orange Cross," the International Jubilee Conference, will be held at The Hague, September 10-12, 1959, under the sponsorship of the Royal National Society for Lifesaving and First Aid to the Injured "The Orange Cross." Her Majesty, Queen Juliana of the Netherlands, is serving as a Patron. The meeting will serve as a means of organizing an international congress in the field of lifesaving work. The main discussion topics will be "Resuscitation," "Burns," and "Electric Shock." For information write, 14, Burgemeester de Monchyplein, The Hague—Netherlands.

THE BRITISH COLUMBIA MEDICAL RESEARCH INSTITUTE

The Vancouver General Hospital on January 1, 1959, became The George F. Strong Research Institute of the University of British Columbia in memory of Dr. George F. Strong, F.A.C.P., who was President of the American College of Physicians in 1955-56.

Dr. Kenneth Evelyn, F.A.C.P., Research Professor of Medicine at the University of British Columbia Faculty of Medicine, Vancouver, B. C., Can., continues as Head of the Institute. Dr. Evelyn was a Research Fellow of the American College of Physicians in 1946.

Personal Notes

At a recent meeting of the American Board of Internal Medicine, Dr. Howard P. Lewis, F.A.C.P., Portland, Ore., President of the American College of Physicians, was elected Chairman of the American Board of Internal Medicine, succeeding Dr. Thomas M. Durant, F.A.C.P., Philadelphia, Pa., Treasurer of the College.

Dr. William Levison, F.A.C.P., Newark, N. J., was recently elected President of the New Jersey Diabetes Association.

Rear Admiral Francis J. Braceland, F.A.C.P., (MC), U. S. Naval Reserve, Hartford, Conn., was Chairman of a section of the Scientific Program of the American Psychiatric Association held in Philadelphia, Pa., April 27-May 1, 1959.

Dr. Richard A. Kern, F.A.C.P., Philadelphia, Pa., Past President of the College, received the Strittmatter Award of the Philadelphia County Medical Society at a meeting held May 13, 1959.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., was recently elected a member of the American Equilibration Society.

Dr. Leo H. Crip, F.A.C.P., Pittsburgh, Pa., presented a paper entitled "Clinical Observations on Bronchial Asthma" before the Annual Session of the Pennsylvania Tuberculosis and Health Society in Scranton, Pa., April 16, 1959. He also discussed "Allergic Factors in Diseases of the Chest" before a meeting of the Staff Executives of the Trudeau Society held in Philadelphia, Pa., March 12, 1959.

Rear Admiral Irwin L. V. Norman, F.A.C.P., Washington, D. C., (MC), U. S. Navy, retired on April 30, 1959, after completing 32 years of service. Since February, 1955, he held two positions, that of Assistant Chief of the Bureau for Personal and Professional Operations, and Inspector General of the Medical Department Activities. During the 2nd World War, he was assigned as Fleet Medical Officer of the 7th Fleet and directed the establishment of dispensaries, base and fleet hospitals, and medical supply depots on the mainland of Australia and advance bases in New Guinea. He received a Letter of Commendation from the Commander in Chief, U. S. Pacific Fleet, for outstanding performance of duty.

Dr. Norman has accepted a position as Medical Director of the Chase Manhattan Bank of New York City. He will reside at 22 Stonehurst Drive, Tenafly, N. J.

Captain Harry A. Weiss, F.A.C.P., (MC) U. S. Navy, formerly stationed at the Naval Hospital in San Diego, Calif., was recently transferred to the Naval Hospital at Yokosuka, Japan.

Dr. Harold C. Lueth, F.A.C.P., Evanston, Ill., was Chairman of the American Medical Association Committee on Disaster Medical Care. The one-day program was featured at the 7th Annual National Civil Defense Conference held at Atlantic City, June 6, 1959. It was presented entirely by the Army Medical Service and dramatized the fact that the medical and health professions can take positive action to minimize the impact of mass casualties if properly trained and organized.

Captain Edward P. McLarney, F.A.C.P., (MC), U. S. Navy, formerly stationed at the Naval Hospital, Memphis, Tenn., was recently transferred to the Camp Pendleton Naval Hospital, Calif.

Dr. George F. Evans, F.A.C.P., Clarksburg, W. Va., President of the West Virginia State Medical Association, was a guest speaker at the monthly meeting of the Preston County Medical Society held in Hopemont, W. Va., February 12, 1959.

Drs. Carl C. Fischer, F.A.C.P., Philadelphia, Pa.; James G. Kramer, F.A.C.P., Akron, Ohio, and Clarence H. Webb, F.A.C.P., Shreveport, La., are members of the Executive Board of the American Academy of Pediatrics which held its annual meeting in San Francisco, Calif., April 13-15, 1959.

Four Fellows of the College were participants in the program of the 161st Annual Meeting of the Medical and Chirurgical Faculty of Maryland at a meeting held in Baltimore, Md., April 15-17, 1959. Dr. William Dameshek, Boston, Mass., discussed the subject, "Leukemia; Present Status," Dr. Charles F. Wilkinson, Jr., New York, N. Y., "Atherogenesis and Lipid Metabolism," and Dr. Edgar V. Allen, Rochester, Minn., "The Natural History of Arteriosclerosis Obliterans (Illustrated)." Dr. J. Sheldon Eastland, Baltimore, Md., President of the Faculty, presided at a medico-legal symposium entitled "Whiplash Injuries: A Conference between the Counsel and Medical Witnesses."

Dr. Herman Beerman, F.A.C.P., Philadelphia, Pa., was Chairman of the Committee on Scientific Programs and a member of the Committee on Arrangements for the 20th Annual Meeting of the Society for Investigative Dermatology held in Atlantic City, N. J., June 6-7, 1959.

Dr. Edward C. Reifenstein, Jr., F.A.C.P., Butler, N. J., presided as President at the 15th Annual Meeting of the American Society for the Study of Sterility held in Atlantic City, N. J., April 3-5, 1959.

Dr. R. Bruce Logue, F.A.C.P., Atlanta, Ga., gave two talks at a recent meeting of the East Tennessee Heart Association in Knoxville, Tenn., and was also elected Chairman of the Sub-specialty Board in Cardiology of the American Board of Internal Medicine.

Dr. Thomas L. Ross, Jr., F.A.C.P., Macon, Ga., was a guest speaker at a recent meeting of the Dublin Chapter of the Georgia Heart Association.

Dr. W. D. Hazlehurst, (Associate), was named Chief Medical Staff Officer and Dr. J. R. S. Mays, F.A.C.P., was named Vice President of the staff of the Macon Hospital, Macon, Ga.

Dr. T. Reid Jones, (Associate), and Dr. M. Donald McFarland, (Associate), both of Kansas, Mo., were named Treasurer and Director of Clinics, respectively, at a recent meeting of the Kansas City Southwest Clinical Society.

Dr. William A. D. Anderson, F.A.C.P., Coral Gables, Fla., was recently appointed a member of the Joint Committee on Cancer Staging and End Results Reporting of the College of American Pathologists. He is also serving as Chairman of the Section on Pathology of the Southern Medical Association.

Dr. M. Jay Flipse, F.A.C.P., Miami, Fla., was one of three Miami physicians who were honored by the members of the Dade County Medical Association for "honorable service during more than 35 years of continuous membership."

Dr. Lawrence E. Putnam, F.A.C.P., Washington, D. C., was elected an alumnus member of Alpha Omega Alpha by the Alpha Chapter at the George Washington University School of Medicine, Washington, D. C.

Dr. Harold N. Neu, F.A.C.P., Omaha, Nebr., was elected President of the Nebraska Society of Internal Medicine recently.

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., addressed the Clinical Session of the Phi Lambda Kappa Fraternity at Miami Beach, Fla., April 6, 1959. He spoke on the "Clinical Value of Chlorpropamide."

Captain George N. Raines, F.A.C.P., (MC), U.S.N., retired recently after 28 years of active service. His last assignment was Head, Neuropsychiatry Branch, Bureau of Medicine and Surgery, Navy Department, Washington, D. C. Since 1940 he served as Professor of Psychiatry and Chairman of the Department of Psychiatry of the Georgetown University School of Medicine.

Five Fellows of the College served as officers of the American College of Cardiology which held its 8th Annual Convention in Philadelphia, Pa., May 25-29, 1959. The members included: Drs. George W. Calver, Washington, D. C., President; Ignacio Chavez, Mexico D.F., Mexico, Vice President; Philip Reichert, New York, N. Y., Secretary-Treasurer; Henry I. Russek, Staten Island, N. Y., Assistant Secretary, and Louis F. Bishop, New York, N. Y., Assistant Treasurer.

Brigadier General M. Samuel White, F.A.C.P., U.S.A.F., (MC), Director, Medical Staffing and Education Office of the Surgeon General, and President of the

Aero Medical Association, Washington, D. C., presided at the 30th Annual Meeting of the Association held in Los Angeles, Calif., April 27-29, 1959. Colonel Harold V. Ellingson, (Associate), U.S.A.F., (MC), Director of Education and Plans, U.S.A.F. School of Aviation Medicine, Randolph Air Force Base, Tex., participated in two symposia entitled "Aeromedical Aspects of Stress" and "Toxicological Health Hazards."

Four members of the College were speakers at the joint meeting of the Montana Heart Association and the Montana Trudeau Society held in Missoula, Mont., April 17-18, 1959. Included were: Dr. Walter M. Kirkendall, F.A.C.P., Clinical Associate Professor of Internal Medicine, State University of Iowa College of Medicine, Iowa City, Iowa; Dr. David T. Smith, F.A.C.P., Professor of Bacteriology and Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C.; Dr. Jay A. Myers, F.A.C.P., Professor of Internal Medicine, Preventive Medicine, and Public Health, University of Minnesota Medical School, Minneapolis, Minn., and Dr. Carroll J. Martin, (Associate), Director, Cardiopulmonary Laboratory, Firland Sanitarium, Seattle, Wash.

Dr. George W. Thorn, F.A.C.P., Hersey Professor of Theory and Practice of Physic, Harvard Medical School, Boston, Mass., and Dr. Carl V. Moore, F.A.C.P., Chairman, Department of Medicine, Washington University School of Medicine, St. Louis, Mo., were guest speakers at the Pittsburgh Bicentennial Lecture Week in Medicine, sponsored by the University of Pittsburgh School of Medicine and held in Pittsburgh, Pa., February 23-27, 1959.

Dr. George E. Armstrong, F.A.C.P., Vice Chancellor for Medical Affairs, New York University, New York, N. Y., was a speaker during the celebration of the 100th Anniversary of the Third (N.Y.U.) Surgical Division of the Bellevue Hospital Center as a part of the New York University College of Medicine Alumni Day Ceremonies held February 21, 1959.

A portrait of Dr. Samuel A. Levine, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School, Boston, Mass., painted by Alfred Jonniaux, was recently presented to the Trustees of the Peter Bent Brigham Hospital by a patient, Mr. James E. Stiles, of Long Island, N. Y., as a tribute to Dr. Levine's contribution to medicine.

Dr. Joseph W. Post, F.A.C.P., Philadelphia, Pa., was recently honored as "Physician of the Year" by the Philadelphia Business Club on the occasion of his 50th year in medicine for "high ideals of humanity shown in the pursuit of his profession." The award was made by Harold E. Stassen, former President of the University of Pennsylvania and Presidential Disarmament Adviser.

Five Fellows of the College participated in the program of the Annual Clinical Conference of the Chicago Medical Society held in Chicago, Ill., March 2-5, 1959. The members included: Drs. William T. Foley, New York, N. Y.; Edgar V. Allen, Rochester, Minn.; Julius L. Wilson, Philadelphia, Pa., John R. Haseric, Cleveland, Ohio, and Stewart G. Wolf, Jr., Oklahoma City, Okla.

Dr. Leroy Burney, F.A.C.P., Surgeon General, U.S.P.H.S., Washington, D. C., discussed the subject, "The Role of Government in the Development of Basic Re-

search," at the Symposium on the Structure of Science sponsored by the Wistar Institute and held in Philadelphia, Pa., April 17-18, 1959. He also was a speaker at the Second National Conference on World Health held in Washington, D. C., May 7-9 and sponsored by the National Citizens Committee for the World Health Organization.

Dr. Richard S. Gubner, F.A.C.P., Clinical Associate Professor of Medicine, State University of New York School of Medicine in New York City; Dr. J. R. Kitchell, F.A.C.P., Chief of Cardiology, Presbyterian Hospital, Philadelphia, Pa.; Dr. Henry A. Peters, F.A.C.P., Associate Professor of Neuropsychiatry, University of Wisconsin School of Medicine, Madison, Wis., and Dr. H. Mitchell Perry, Jr., Assistant Professor of Medicine, Washington University School of Medicine, St. Louis, Mo., were participants in the Symposium on Metal-Binding in Medicine, sponsored by the Hahnemann Medical College and Hospital of Philadelphia and held in Philadelphia, May 6-8, 1959.

Dr. Robert J. Hasterlick, F.A.C.P., member of the staff of the Argonne Cancer Research Hospital of the University of Chicago, Ill.; Dr. Gould A. Andrews, F.A.C.P., member of the staff of the Oak Ridge Institute of Nuclear Studies, and Commander William McFarland, (Associate), (MC), U.S.N., U. S. Naval Hospital, Bethesda, Md., were speakers at the 2nd Symposium on Advances in Nuclear Medicine sponsored by the U. S. Medical Center, Bethesda, Md.

Dr. Edward H. Morgan, F.A.C.P., Clinical Assistant Professor of Medicine, University of Washington Medical School, Seattle, Wash., was a guest speaker at the Alaska State Medical Association Meeting held in Juneau, Alaska, March 19-21, 1959.

Dr. Edgar G. Givhan, Jr., F.A.C.P., Birmingham, Alabama, presided as President of the Association at the Annual Session of the Medical Association of the State of Alabama held in Birmingham, Ala., April 9-11, 1959. Dr. Sara M. Jordan, F.A.C.P., Boston, Mass., presented the Jerome Cochran Lecture on the subject, "Somatospsychic Medicine."

Dr. Edward D. Freis, F.A.C.P., Associate Professor of Medicine, Georgetown University School of Medicine, Washington, D. C., was recently elected Chairman-Elect of the Council on High Blood Pressure Research of the American Heart Association.

Dr. William G. Sauer, F.A.C.P., Rochester, Minn., discussed the subject, "Facial Enteritis: An Unusual Cause of Intestinal Obstruction, Chronic Blood Loss, or Malabsorption Syndrome," at the annual meeting of the Iowa State Medical Society held in Des Moines, Iowa, April 19-22, 1959.

Three Fellows of the College were program participants at the 71st Annual Meeting of the American Association of Railway Surgeons held in Chicago, Ill., April 16-18, 1959. Dr. David I. Abramson, Chicago, Ill., was moderator of a symposium on "Peripheral Vascular Diseases"; Dr. Clifford J. Barborka, Chicago, Ill., was a moderator of the symposium entitled "Problems in the Management of Peptic Ulcer"; and Dr. Richard D. McKenna, Montreal, Canada, was a participant in a program devoted to the discussion of gastroenterology.

Dr. Maurice A. Schnitker, F.A.C.P., Toledo, Ohio, was moderator of a panel discussion on the subject of "Hypertension" at the annual meeting of the Ohio State Medical Association held in Columbus, Ohio, April 21-24, 1959.

Dr. Harold G. Wolff, F.A.C.P., Professor of Medicine (Neurology) and Associate Professor of Psychiatry, Cornell University Medical College, New York, N. Y., discussed the subject "Headache" at the annual Bernard Comroe lecture sponsored by the Kappa Pi Chapter of the Phi Delta Epsilon Fraternity held at the University of Pennsylvania Medical School March 20, 1959.

Dr. Franz K. Bauer, F.A.C.P., Los Angeles, Calif., presented a paper on "Thyroid Cancer" at a Symposium on Radioisotope Scanning sponsored by the International Atomic Energy Agency and the World Health Organization and held at Vienna, Austria.

Dr. Alfred Ebel, F.A.C.P., New York, N. Y., discussed the subject, "Skin Thermometry in the Diagnosis of Peripheral Vascular Diseases," and Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., "The 3rd International Congress of Physical Medicine," at the meeting of the Eastern Section of the American Congress of Physical Medicine and Rehabilitation held at New Haven, Conn., April 18, 1959.

Dr. Robert B. Kerr, F.A.C.P., Professor of Medicine at the University of British Columbia Faculty of Medicine, Vancouver, B. C., Can., has been appointed the Sir Arthur Sims Commonwealth Traveling Professor for 1959. His assignment will comprise teaching in the Faculties of Medicine at the Union of South Africa, Rhodesia, Nigeria, Ghana, Uganda, Kenya, and Malta. Dr. Kerr will return to Vancouver at the end of August, 1959.

Three Fellows of the College were guest speakers at the 53rd Annual Meeting of the Oklahoma State Medical Association held in Tulsa, Okla., April 20-22, 1959. Included were Drs. E. Perry McCullagh, Cleveland, Ohio; William D. Davis, Jr., New Orleans, La.; and Clark H. Millikan, Rochester, Minn.

Dr. Alexander B. Gutman, Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y., gave the Annual John Auer Lecture at the St. Louis University School of Medicine on March 13, 1959. The lecture was sponsored by the Phi Beta Pi Fraternity.

Five Fellows of the College from Philadelphia, Pa., were participants in the Annual Meeting of the Pennsylvania Tuberculosis and Health Society conducted in collaboration with the Pennsylvania Trudeau Society, the Pennsylvania Chapter of the American College of Chest Physicians and the Pennsylvania Conference of Tuberculosis Workers and held in Scranton, Pa., April 15-17, 1959. The Fellows and their subjects were: Dr. Henry P. Close, "Emphysema"; Dr. Samuel C. Stein, "Tuberculosis"; Drs. Robert L. Mayock and Harold L. Israel, "Other Acute Respiratory Diseases," and Dr. David A. Cooper presided at a discussion on "Consecutive Case Conference."

Dr. Joseph T. Beardwood, Jr., F.A.C.P., Director of Medical Services, Abington Memorial Hospital, Philadelphia, Pa., presided at the Third Annual Medical Symposium sponsored by the Hospital on the subject, "Steroid Therapy—Values and Limitations," and held on May 20, 1959.

Dr. Harry J. Hurley, Jr., (Associate), Newtown Square, Pa., was recently appointed Professor of Dermatology at the Hahnemann Medical College of Philadelphia.

Five Fellows of the College were guest speakers at the 92nd Annual Session of the Texas Medical Association held in San Antonio, Texas, April 18-21, 1959. Included were Drs. Walter C. Alvarez, Chicago, Ill.; George C. Andrews, Jr., New York, N. Y.; Richard J. Bing, St. Louis, Mo.; Grace A. Goldsmith, New Orleans, La.; and Oscar A. Sander, Milwaukee, Wis.

Dr. Elliot V. Newman, F.A.C.P., Professor of Experimental Medicine, Vanderbilt University School of Medicine, Nashville, Tenn., discussed the subject, "Regulation of Electrolytes in the Management of Heart Disease," and Dr. Julian M. Ruffin, F.A.C.P., Professor of Medicine, Duke University School of Medicine, Durham, N. C., discussed "Recognition and Management of Steatorrhea," at the Symposium on Nutritional Problems in Medicine sponsored by the American Medical Association's Council on Foods and Nutrition and the Vanderbilt University School of Medicine and held at Nashville, Tenn., May 8, 1959.

Three Fellows of the College were speakers at the Annual Meeting of Virginia Trudeau Society held in Richmond, Va., April 8, 1959. The members and their subjects were as follows: Dr. Oscar Auerbach, Chief of Laboratory Services, Veterans Administration Hospital, East Orange, N. J., "Carcinoma-in-Situ and Its Significant Changes"; Dr. Sydney Jacobs, New Orleans, La., President-Elect of the Southern Tuberculosis Conference, "Unusual Forms of Pneumonia and Diagnosis and Treatment Thereof"; Dr. Daniel E. Jenkins, Professor of Medicine, Baylor University College of Medicine, Houston, Tex., President of the American Trudeau Society, gave the keynote address.

Three members of the College were speakers on the program of the Mid-Tide-water Medical Society held at West Point, Va., January 27, 1959. The members and their subjects were: Dr. John L. Guerrant, F.A.C.P., Charlottesville, Va., "Medical Management of Pulmonary Infections"; Dr. George Minor, F.A.C.P., Washington, D. C., "The Surgical Management of Dysphagia"; and Dr. James C. Respess, (Associate), Charlottesville, Va., "Dysphagia."

Dr. William R. Jordan, F.A.C.P., Richmond, Va., presided as President of the Tri-State Medical Association at the Annual Meeting of the Association held in Winston-Salem, N. C., March 16-17, 1959.

Dr. Arthur Haut, (Associate), Instructor at the University of Utah College of Medicine, Salt Lake City, Utah, was appointed one of twenty-five Markle Scholars in Medical Science by the John and Mary R. Markle Foundation of New York, N. Y. Each appointment carried with it a grant of \$30,000.00 appropriated to the medical

school where the scholar teaches and does research, to be used toward his support and to aid his research.

Five Fellows of the College were recently named to the Committee of the National Foundation. The Committee will counsel the Foundation on allocations for clinical research and medical care as a part of its expanded program which now includes arthritis and birth defects in addition to polio. Drs. Robert F. Pitts, New York, N. Y., Charles A. Ragan, Jr., New York, N. Y., and John E. Deitrick, New York, N. Y., were named members of the Committee on Clinical Investigation, and Drs. Walter Bauer, Boston, Mass., and Howard A. Rusk, New York, N. Y., were appointed members of the Committee on Clinical Care.

Dr. Theodore Rothman, F.A.C.P., Beverly Hills, Calif., was Secretary of the Session on History and Culture of the American Psychiatric Association at its meeting in Philadelphia, Pa., April 27-May 1, 1959.

Dr. Andrew L. Banya, F.A.C.P., Chicago, Ill., has been appointed a member of the Advisory Committee on Chest Diseases and Chairman of the respective Sub-Committee on Research of the State of Illinois Department of Public Welfare.

Brigadier General M. S. White, F.A.C.P., U.S.A.F. (MC), President of the Aero Medical Association, and Director of Medical Staffing and Education, Office of the Surgeon General, U.S.A.F., gave the Annual Alpha Omega Alpha address at the New York University College of Medicine on April 3, 1959. His subject was "The Significance of Aerospace Medicine to the Medical Graduate of Today." On April 8, 1959, he presented the Twelfth Walter Estell Lee Lecture at the University of Pennsylvania Graduate School of Medicine. His subject was "Aerospace Medicine in the Clinical Specialties." General White became Surgeon of the Air Training Command on June 30, 1959.

Dr. Mary H. Easby, F.A.C.P., Philadelphia, Pa., Chief of the Cardiac Clinic at the Woman's Hospital of Philadelphia, retired on May 1, 1959, after 35 years in the field of medicine. She joined the staff of the Woman's Hospital in 1930 and in 1952 she established Pennsylvania's first "heart kitchen" under the auspices of the Woman's Hospital Forum.

Dr. Dale P. Osborn, Sr., F.A.C.P., Cincinnati, Ohio, was named President-Elect of the Ohio State Heart Association recently at a meeting held in Columbus, Ohio. Dr. Osborn, who will take office as President next April, is a former President and Member of the Council of the Cincinnati Academy of Medicine; a Member of the Board of Trustees of the Heart Association of Cincinnati, and a Member of the Assembly Planning Committee of the American Heart Association.

Dr. LeRoy Sante, F.A.C.P., Professor of Radiology and Director of the Department, St. Louis University School of Medicine, was one of three radiologists to receive a gold medal award from the American College of Radiology at a recent meeting of the College. The award is presented "for distinguished and extraordinary service to the American College of Radiology and to the profession for which it stands."

Dr. John J. Hammond, (Associate), Assistant Professor of Clinical Medicine at the St. Louis University School of Medicine, St. Louis, Mo., was recently appointed Chief of the Medical Department at St. John's Hospital.

Dr. John S. Chambers, F.A.C.P., Director of University Health Service and Professor of Hygiene and Public Health, University of Kentucky, Lexington, Ky., was reelected President at a recent meeting of the Kentucky Medical Foundation.

Dr. John W. Norcross, F.A.C.P., Boston, Mass., was a participant in the Lahey Clinic Fellowship Lectures held April 29, 1959, on the subject of Isotopes.

Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., discussed the subject, "Some Interesting Cases of Pericardial Disease: Roentgenologic and Clinical Aspects," at a sectional meeting of the American College of Cardiology held in Boston, Mass., April 14, 1959.

Dr. Robert H. Felix, F.A.C.P., Bethesda, Md., participated in a Conference on Experimental Psychiatry held in Pittsburgh, Pa., March 5-7, 1959, and sponsored by the Western Psychiatric Institute and Clinic.

Two Fellows and three Associates from Boston, Mass., were participants in a meeting of the New England Cardiovascular Society held in Boston, March 9, 1959. The Fellows, Drs. Lewis Dexter and Herman L. Blumgart, presided at the Scientific Sessions. Drs. Richard Gorlin, Roger B. Hickler, and David M. Travis, all Associates, were speakers on the program.

A postgraduate course entitled "Advances in Internal Medicine" was held at the United States Air Force Hospital, Lackland Air Force Base, San Antonio, Tex., April 6-10, 1959. The course was sponsored by the Department of Medicine at Lackland, with Colonel Philip G. Keil, F.A.C.P., U.S.A.F. (MC), serving as Chairman, and Major John W. Ord, (Associate), U.S.A.F. (MC), as Course Director. The instruction was given in conjunction with the visit of Dr. William B. Bean, F.A.C.P., Professor and Head of Department of Internal Medicine, State University of Iowa College of Medicine, Iowa City, Iowa, as Distinguished Visiting Lecturer.

Other College members serving as faculty were Dr. Carleton B. Chapman, F.A.C.P., Professor of Medicine, University of Texas Southwestern Medical School, Dallas, Tex.; Drs. Robert A. Hettig, F.A.C.P., and Ellard M. Yow, F.A.C.P., both Professors of Internal Medicine at Baylor University College of Medicine, Houston, Tex.; Dr. Julian C. Barton, F.A.C.P., and Dr. Sydney Schiffer, F.A.C.P., both of San Antonio, Tex., and both Civilian Consultants in Internal Medicine to the U.S.A.F. Hospital, Lackland; Major Paul E. Teschan, (Associate), (MC), U.S.A., and Lt. Col. Norman M. Scott, (Associate), (MC), U.S.A., both Staff Members at the Brooke Army Hospital, Fort Sam Houston, Tex.; Colonel James T. Hardy, U.S.A.F., (MC); Lt. Col. Wilbur L. Kenoyer, U.S.A.F. (MC); Lt. Col. Robert B. Stonehill, U.S.A.F. (MC); Major Joseph T. Melton, U.S.A.F. (MC); Major Joel E. Reed, U.S.A.F. (MC), and Major Carmault B. Jackson, U.S.A.F. (MC), all Associates and Members of the Lackland Hospital Staff.

AUDITOR'S REPORT, YEAR ENDING DECEMBER 31, 1958

To the Board of Regents
 American College of Physicians
 4200 Pine Street
 Philadelphia 4, Pennsylvania

Mr. E. R. Loveland, Executive Secretary

Dear Sir:

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC.

for the year ending December 31, 1958, and the accompanying statements, including the Balance Sheet at December 31, 1958, the analyses of the General Fund and the Endowment Fund and the Statement of Income Account for the Calendar Year 1958 are in accordance with the Books of Account, and in my opinion present fairly the financial position at December 31, 1958 and the results of operations for the calendar year 1958, in conformity with generally accepted accounting principles applied on a basis consistent with that of preceding years, and subject to the following comments:

Cash: The cash was properly accounted for, was confirmed by direct correspondence with the following depositories, and the Petty Cash verified:

| | |
|--|---------------------|
| Girard Trust Corn Exchange Bank, Philadelphia | \$133,986.82 |
| Provident Tradesmen's Bank & Trust, Philadelphia | 30,137.87 |
| Philadelphia Saving Fund Society, Philadelphia | 40,600.00 |
| Royal Bank of Canada, Montreal, Que., Canada | 8,046.52 |
| Petty Cash | 275.00 |
| | <u>\$213,046.21</u> |

Accounts Receivable: The Accounts Receivable were examined and found to be less than one year old and appear to be collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments: The securities were accounted for by direct correspondence, and the income for the period under review was verified. The investment transactions are recorded properly in the general books of account and in the Investment Ledger, which is in agreement with the investment accounts of the General Ledger.

General: The changes in the amount of the Endowment Fund and the General Fund during the year 1958 are as follows:

| | Balance Jan. 1, 1958 | Balance Dec. 31, 1958 | Increase |
|--|-------------------------|--------------------------|---------------------|
| Endowment Fund | \$ 520,777.89 | \$ 703,035.39 | \$182,257.50 |
| James D. Bruce Fund | 10,000.00 | 10,000.00 | |
| A. Blaine Brower Fund | 20,100.00 | 20,100.00 | |
| Willard O. Thompson Fund | 10,466.58 | 10,466.58 | |
| General Fund | 872,169.00 | 909,228.19 | 37,059.19 |
| Restricted Funds | 2,402.04 | 3,396.13 | 994.09 |
| Residency Revolving Loan Fund | 60,000.00 | 60,104.00 | 104.00 |
| Southern Calif. Scholarship Fund | | 4,600.00 | 4,600.00 |
| | <u>\$1,495,915.51</u> | <u>\$1,720,930.29</u> | <u>\$225,014.78</u> |

The Executive Secretary has analyzed the income of the ANNALS OF INTERNAL MEDICINE according to Volume, so that the income and expenses are stated according to the year of publication, with the exception of Volumes of prior years, which are closed out and not carried in an inventory account, with the sales properly credited to the General Fund according to the date of sale.

General Comments: The prepaid insurance at December 31, 1958, was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the Furniture and Equipment Accounts represent proper additions to the account, and the allowances for depreciation appear to be adequate. A depreciation reserve account has been set up for the Headquarters Building in accordance with the action of the Board of Regents at the meeting of December 12, 1937, which provided that depreciation on the building should be taken into account at the rate of \$1,000.00 per year and increased in 1949 to \$2,000.00. A depreciation reserve account has been set up for 404-12 S. 42nd Street at the rate of \$500.00 per year. The footings and extensions of the inventory were verified.

All ascertainable liabilities have been included in the Balance Sheet.

All recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in banks and all disbursements, as indicated on the vouchers, cancelled checks and bank statements, were properly recorded in the books of account.

Respectfully submitted,

(Signed) DAVID ROBIN, *Auditor*

AMERICAN COLLEGE OF PHYSICIANS, INC.—Balance Sheet, December 31, 1958

| | GENERAL FUND | COLLEGE NEWS NOTES | July 1959 |
|--|----------------------|--------------------|-----------|
| <i>Assets</i> | | | |
| <i>Current:</i> | | | |
| Cash in banks and on hand | \$ 56,876.22 | | |
| Accounts Receivable | 34,764.92 | | |
| American Airlines | 425.00 | | |
| Inventory of Keys, Pledges and Frames | 1,455.96 | | |
| Accrued Income on Endowment Fund Investments | 3,743.34 | | |
| Accrued Income on General Fund Investments | 2,801.90 | | |
| Investments at Book Value | 888,295.09 | | |
| Insurance Deposit | 555.00 | | |
| | <u>\$ 988,917.43</u> | | |
| <i>Deferred:</i> | | | |
| Expenses, 40th Annual Session | \$ 14,302.22 | | |
| Expenses, 41st Annual Session | 530.28 | | |
| Advertising, Volume 50 | 23.94 | | |
| | <u>14,856.44</u> | | |
| <i>Fixed:</i> | | | |
| College Headquarters | \$112,882.32 | | |
| Less: Depreciation | 32,000.00 | | |
| Furniture and Equipment | \$ 26,456.51 | | |
| Less: Depreciation | \$ 13,131.74 | | |
| 40-12 S. 42nd Street | \$ 14,144.72 | | |
| Less: Depreciation | 2,000.00 | | |
| | <u>12,144.72</u> | | |
| | | | |
| <i>Endowment Fund</i> | | | |
| <i>Assets</i> | | | |
| <i>Current:</i> | | | |
| Cash, Provident Tradesmen's Bank | \$ 85,432.12 | | |
| Cash, Phila. Saving Fund Society | 30,157.87 | | |
| | <u>40,600.00</u> | | |
| Investments at Book Value | \$ 156,169.99 | | |
| Accrued Income on Investments | 592,031.98 | | |
| | <u>3,743.34</u> | | |
| | <u>\$ 751,945.31</u> | | |
| <i>Liabilities</i> | | | |
| Endowment Fund, Principal | | \$ 703,035.39 | |
| Accrued Income, Due to General Fund | | 3,743.34 | |
| JAMES D. BRUCE FUND | | 10,000.00 | |
| A. BLAINE BROWER FUND | | 20,100.00 | |
| WILLARD O. THOMPSON TRAVELING SCHOLARSHIP FUND | | 10,466.58 | |
| SOUTHERN CALIFORNIA TRAVELING SCHOLARSHIP FUND | | 4,600.00 | |
| | <u>\$ 751,945.31</u> | | |

*Summary of Operations for the Calendar Year 1958**Income:*

| | |
|---|--------------|
| Annual Dues | \$ 99,347.62 |
| Initiation Fees | 23,650.00 |
| Subscriptions, ANNALS OF INTERNAL MEDICINE | 184,346.64 |
| Advertising, ANNALS OF INTERNAL MEDICINE | 274,762.55 |
| Income from Investments, General Fund (including Accrued) | 43,873.04 |
| Income from Investments, Endowment Fund (including Accrued) | 26,007.50 |
| Dividend on Perpetual Insurance Deposit | 60.00 |
| Income on Sale of ANNALS Volume Files | 507.19 |
| Postgraduate Courses (Balance) | 12,922.42 |
| Profit on Sale or Maturity of Securities, General Fund | 8,363.85 |
| Interest on Time Deposits, General Fund | 899.10 |
| 404-12 S. 42nd Street, Contributions | 2,160.00 |
| Thirty-ninth Annual Session: | |
| Banquet Balance | \$ 362.02 |
| Exhibits | 51,265.86 |
| Guest Fees | 7,715.00 |
| | 59,342.88 |
| Cumulative Index Sales | 226.58 |
| 1957 Supplement Sales | 101.60 |
| Keys, Pledges and Frames | 79.78 |
| Profit on Equipment Traded In | 35.00 |
| | \$736,685.75 |

Expenses:

| | |
|--|--------------|
| Salaries | \$125,868.70 |
| Communications | 22,805.48 |
| Office Supplies and Stationery | 4,393.50 |
| Printing | 205,925.39 |
| Maintenance | 366.93 |
| Traveling Expenses | 32,899.33 |
| Editorial Assistance | 1,487.60 |
| Miscellaneous | 4,111.56 |
| College Headquarters, Maintenance, Taxes, Insurance, etc. | 8,313.70 |
| Depreciation on College Headquarters Building | 2,000.00 |
| Depreciation on 404-12 S. 42nd Street | 500.00 |
| Associated Hospital Service (Blue Cross and Blue Shield) | 811.48 |
| Regional Meetings | 8,780.19 |
| Depreciation on Furniture and Equipment | 3,316.02 |
| John Phillips Memorial Award | 415.76 |
| Investment Counsel Service and Security Custodian's Fee | 2,266.00 |
| Employees' Pension Fund | 3,721.03 |
| Advertising Discounts | 5,761.82 |
| Joint Commission on Accreditation of Hospitals | 29,976.44 |
| Academic Regalia | 591.85 |
| Interlingua Translations | 797.80 |
| 1958 Supplement to the 1955 Directory | 3,901.57 |
| Research Fellowships | 25,200.00 |
| Committee on Insurance | 1,043.61 |
| World Medical Association | 100.00 |
| Collection and Exchange | 62.00 |
| Social Security Taxes | 2,021.73 |
| Travel Accident Insurance | 350.00 |
| Annals Profit to Endowment Fund | 150,000.00 |
| Forwarded | \$647,789.49 |
| | \$736,685.75 |

| | |
|--|-----------------------|
| <i>Income</i> , Brought Forward | \$ 736,685.75 |
| <i>Expenses</i> , Brought Forward | \$ 647,789.49 |
| Thirty-Ninth Annual Session—Special Expenses: | |
| Committee on Panel Discussions | \$ 57.90 |
| Committee on Publicity | 1,128.18 |
| Committee on Ladies' Entertainment | 2,261.89 |
| Convocation | 1,546.45 |
| Pre-Convocation Dinner | 201.85 |
| Regents-Governors Dinner | 2,499.46 |
| Regents-Governors Luncheon | 338.10 |
| Reception for New Members | 1,724.75 |
| Registration | 974.98 |
| Equipment Rental | 1,086.00 |
| Rent | 4,809.00 |
| Projection Service | 2,081.90 |
| College Booth Expenses | 483.04 |
| Public Address System | 2,180.20 |
| Reporting | 605.00 |
| 1958 Scientific Exhibits | 78.85 |
| Badges | 429.25 |
| Televised Clinics | 426.37 |
| Guard Service and Stage Hands | 1,483.73 \$ 24,396.90 |
| 404-12 S. 42nd Street: | |
| Heat, Light, Gas and Water | \$ 70.17 \$ 70.17 |
| TOTAL EXPENSES | |
| Net Income for 1958 Credited to General Fund | |
| <u>\$ 672,256.56</u> | |
| <u>\$ 64,429.19</u> | |

INVESTMENTS

BONDS

At December 31, 1958

| Par Value | Bonds | Funds | |
|-----------|---|--------------|--------------|
| | | Endowment | General |
| \$15,000 | Allied Chemical & Dye Corp., Deb. 3½'s, 1978 | \$ 14,850.00 | \$ 9,962.50 |
| 10,000 | Allied Chemical & Dye Corp., Deb. 3½'s, 1978 | | 13,276.25 |
| 13,000 | Aluminum Co. of Canada, Deb. 3½'s, 1970 | | |
| 12,000 | American Electric Power Co., Deb. 3½'s, 1977 | 12,270.00 | 25,156.25 |
| 25,000 | American Telephone & Telegraph, Deb. 4½'s, 1985 | | |
| 43,000 | American Telephone & Telegraph, Deb. 5%, 1983 | 43,628.23 | |
| 30,000 | American Telephone & Telegraph, Deb. 4½'s, 1985 | 30,187.50 | |
| 13,000 | American Telephone & Telegraph, Deb. 3½'s, 1990 | | 12,902.50 |
| 12,000 | American Telephone & Telegraph, Deb. 3½'s, 1990 | 11,910.00 | |
| 9,000 | American Tobacco Co., Deb. 3's, 1969 | 9,415.24 | |
| 14,000 | American Tobacco Co., Deb. 3½'s, 1977 | 14,087.50 | |
| 10,000 | Arkansas Power & Light Co., 1st, 3½'s, 1982 | | 10,367.00 |
| 15,000 | Baltimore & Ohio Equip. Trusts, 3½'s, 1962 | | 14,999.85 |
| 9,000 | Carolina Clinchfield & Ohio Rwy. Co., 1st Mort. 4's, "A", 1965 | 9,465.70 | |
| 10,000 | Chesapeake & Ohio Rwy. Equip. Trust Certs., 2½'s, 1965 | | 9,854.18 |
| 12,500 | Columbia Gas System, Inc., Deb. 3½'s, "C", 1977 | | 12,500.00 |
| 2,500 | Columbia Gas System, Inc., Deb. 3½'s, "C", 1977 | 2,500.00 | |
| 10,000 | Connecting Rwy. Co., 1st, 3½'s, "A", 1976 | 9,600.00 | |
| 10,000 | Connecting Rwy. Co., 1st, 3½'s, "A", 1976 | | 8,925.00 |
| 6,000 | Consolidated Edison Co. of New York, First & Refunding, 3's, 1981 | 5,970.00 | |
| 25,000 | Consolidated Edison Co. of New York, 4¼'s, 1st Mort., "M", 1986 | | 25,218.75 |
| 25,000 | General Electric Co., 3½'s, 1976 | | 24,937.50 |
| 25,000 | General Motors Acceptance Corp., Deb. 3½'s, 1961 | 25,593.75 | |
| 10,000 | General Motors Corp., Deb. 3½'s, 25 yr., 1979 | 10,162.50 | |
| 20,000 | Hydro Electric Power Commission of Ontario, Can., 3½'s, 1979 | 20,675.00 | |
| 15,000 | International Bank for Reconstruction & Dev., 4½'s, 1973 | | 15,056.25 |
| 15,000 | New York Central Railroad Second Equip. Trust Certs., 3½'s, 1965 | | 14,794.13 |
| 1,600 | Niagara Mohawk Power Corp., Deb. 4½'s, 1972 | 1,600.00 | |
| 800 | Niagara Mohawk Power Corp., Deb. 4½'s, 1972 | | 800.00 |
| 5,000 | Oregon-Washington RR & Nav. Co., 1st, 3's, "A", 1960 | 5,300.00 | |
| 4,000 | Oregon-Washington RR & Nav. Co., 1st, 3's, "A", 1960 | | 4,240.00 |
| 20,000 | Pennsylvania RR Equip. Trust Cert., 2½'s, 1961 | | 19,700.00 |
| 15,000 | Pittsburgh & Lake Erie RR, Equip. Trust Certs., 3's, 1964 | | |
| 25,000 | Public Service Electric & Gas, 4½'s, 1986 | | 14,723.04 |
| 10,000 | Reading Co., Equip. Trust Certs., "U", 3½'s, 1963 | | 25,314.25 |
| 3,700 | Scott Paper Co., Deb. 3's, 1971 | | 9,999.90 |
| 10,000 | Seaboard Airline Rwy. Equip. Trusts, 2½'s, "L", 1966 | | 3,700.00 |
| 10,000 | Service Pipeline Co., Deb. 3.20's, 1982 | 10,025.00 | 9,746.80 |
| 15,000 | St. Louis, San Francisco RR Co., Equip. Trusts, 2½'s, 1962, Series "K", 2.925% Basis | | 14,935.53 |
| | Forwarded | \$237,240.42 | \$301,109.68 |

INVESTMENTS—Continued

BONDS

| <i>Par Value</i> | <i>Bonds</i> | <i>Funds</i> | |
|------------------|--|----------------------------|----------------------------|
| | | <i>Endowment</i> | <i>General</i> |
| \$10,000 | Brought Forward | \$237,240.42 | \$301,109.68 |
| | Texas & New Orleans RR Co., 1st & Ref., 3½'s "B", 1970 | 10,458.60 | |
| 10,000 | U. S. Treasury Bonds, 2½'s, "G", March 1, 1959 | 10,000.00 | |
| 6,000 | U. S. Treasury Bonds, 2½'s, "G", July 1, 1959 | 6,000.00 | |
| 2,500 | U. S. Treasury Bonds, 2½'s, "G", March 1, 1960 | 2,500.00 | |
| 2,500 | U. S. Treasury Bonds, 2½'s, "G", January 1, 1961 | 2,500.00 | |
| 2,500 | U. S. Treasury Bonds, 2½'s, "G", January 1, 1962 | 2,500.00 | |
| 30,000 | U. S. Treasury Bonds, 3%, August 15, 1966 | 30,900.00 | |
| 14,000 | U. S. Treasury Bonds, Series "K", September 1, 1966 | 14,000.00 | |
| 20,000 | U. S. Treasury Bonds, Series "K", December 1, 1966 | 20,000.00 | |
| 10,000 | U. S. Treasury Bonds, Series "K", June 1, 1967 | 10,000.00 | |
| 2,500 | U. S. Treasury Bonds, 2½'s, "G", June 1, 1962 | 2,500.00 | |
| 9,000 | West Penn Electric Co., S.F., Coll. Trs. 3½'s, 1974 | 9,541.37 | |
| | Total Bonds | <u><u>\$328,140.39</u></u> | <u><u>\$331,109.68</u></u> |

INVESTMENTS

STOCKS

At December 31, 1958

| <i>Shares</i> | <i>Stocks</i> | <i>Endowment</i> | <i>Funds</i> |
|---------------|---|------------------|----------------|
| | | | <i>General</i> |
| 100 | Aluminum Co. of America, Common | \$ 10,095.05 | |
| 300 | American Can Co., Common | 11,426.84 | |
| 328 | American Power Corp., Common | 4,035.03 | |
| 538 | American Power Corp., Common | | 6,403.09 |
| 100 | American Smelting & Refining Co., 7% Pfd. | 18,867.80 | |
| 33 | American Telephone & Telegraph Co. | 5,846.25 | |
| 110 | American Telephone & Telegraph Co. | | 19,437.50 |
| 800 | Atchison, Topeka & Santa Fe RR Co. | 9,770.74 | |
| 200 | Atchison, Topeka & Santa Fe RR Co. | | 2,442.69 |
| 519 | Atlantic City Electric Company, Common | | 6,488.66 |
| 174 | Atlantic City Electric Company, Common | 1,655.75 | |
| 100 | Bethlehem Steel, 7% Pfd. | 16,825.75 | |
| 327 | Burroughs Corp., Common | | 13,174.88 |
| 260 | Campbell Soup Co., Common | 10,330.06 | |
| 15 | Campbell Soup Co., Common | | 595.97 |
| 150 | Chase Manhattan Bank of New York, Common | 5,039.67 | |
| 178 | Chase Manhattan Bank of New York, Common | 5,596.38 | |
| 214 | Commonwealth Edison Corp., Common | | 5,725.00 |
| 214 | Commonwealth Edison Corp., Common | | 7,593.24 |
| 300 | Consolidated Edison Co. of New York | | 9,979.85 |
| 100 | Consumers Power Co., 4½'s Cum. Pfd. | | 11,287.50 |
| 313 | Dow Chemical Co., Common | | 16,733.97 |
| 200 | E. I. du Pont de Nemours, Common | | 8,714.85 |
| 300 | Firstamerican Corp. ((Stock Dividend)) | | |
| 193 | First National City Bank of New York | | 8,844.29 |
| 389 | First National City Bank of New York | 19,999.85 | |
| 287 | First Pennsylvania Banking & Trust Co. | | 10,132.56 |
| 77 | First Pennsylvania Banking & Trust Co. | 3,170.27 | |
| 300 | General Electric Co., Common | | 3,571.78 |
| 300 | General Electric Co., Common | 3,780.96 | |
| 300 | General Food Corp. | | 23,840.70 |
| 450 | General Motors Corp., Common | | 3,594.53 |
| 180 | General Motors Corp., Common | 2,272.73 | |
| 200 | B. F. Goodrich Tire Co., Common | | 7,830.39 |
| 292 | Gulf Oil Corp., Common | | 8,632.27 |
| 360 | Guaranty Trust Co. of New York, Common | | 19,890.20 |
| 346 | Insurance Company of North America, Common | 10,369.89 | |
| 50 | International Harvester Co. 7% Pfd. | 8,169.00 | |
| 263 | International Paper Co., Common | | 9,356.78 |
| 50 | Kaiser Aluminum & Chemical Co., 4.75 Cum. Pfd. | 2,638.56 | |
| 350 | Kaiser Aluminum & Chemical Co., 4.75 Cum. Pfd. | | 18,434.25 |
| 100 | Mead Corp., 4½'s, Cum. Pfd. | | 9,308.25 |
| 100 | Mead Corp., 4¼'s, Cum. Pfd. | 9,796.05 | |
| 204 | Mellon National Bank | | 17,075.00 |
| 425 | Middle South Utilities, Inc., Common | 8,209.41 | |
| 375 | Middle South Utilities, Inc., Common | | 8,192.35 |
| 318 | Monsanto Chemical Co. | | 8,556.66 |
| 159 | Monsanto Chemical Co., Common | 5,056.95 | |
| 400 | New York State Electric & Gas Co. | | 9,816.02 |
| 50 | Niagara Mohawk Power Corp., 3.90% Pfd. | | 5,067.50 |
| | Forwarded | \$151,431.10 | \$302,242.62 |

INVESTMENTS—Continued

STOCKS

| <i>Shares</i> | <i>Stocks</i> | <i>Endowment</i> | <i>Funds</i> |
|---------------|---|------------------|--------------|
| | Brought Forward | \$151,431.10 | \$302,242.62 |
| 400 | Niagara Mohawk Power Corp., Common | 9,944.61 | 10,627.92 |
| 400 | Niagara Mohawk Power Corp., Common | 10,185.00 | 14,405.25 |
| 100 | Niagara Mohawk Power Corp., 3.60% Pfd. | 5,364.40 | 9,845.45 |
| 330 | Ohio Edison Co., Common | 4,907.09 | 13,557.14 |
| 200 | Owens-Illinois Glass Co., Common | 20,271.43 | 10,157.25 |
| 100 | Owens-Illinois Glass Co., Common | 8,512.85 | 11,456.43 |
| 400 | Pacific Gas & Electric Co., 6% Pfd. | 17,143.94 | 4,300.25 |
| 130 | Pacific Gas & Electric Co., 6% Pfd. | 8,371.18 | 5,286.27 |
| 200 | Panhandle Eastern Pipe Line Co., 4% Cum. Pfd. | 10,924.64 | 10,805.93 |
| 300 | Parke Davis & Company | 12,382.11 | 20,912.79 |
| 210 | Pennsylvania Power & Light Co., Common | 6,146.98 | 18,580.34 |
| 340 | Pennsylvania Power & Light Co., Common | 15,308.43 | 19,829.78 |
| 200 | J. C. Penney Co., Common | 15,450.20 | 5,180.62 |
| 143 | Philadelphia Electric Co., Common | | 10,964.16 |
| 336 | Philadelphia Electric Co., 1.00 Div. Pref. Common | | 19,680.70 |
| 400 | Phillips Petroleum Co., Common | | 9,908.15 |
| 210 | Pittsburgh Plate Glass Co., Common | | 12,858.75 |
| 300 | Republic Steel Corp. | | 3,019.88 |
| 450 | Scott Paper Co., Common | | 11,113.36 |
| 200 | Sherwin-Williams Co., Common | | |
| 1200 | Southern California Edison Co., 4.23% Cum. Pfd. | \$263,891.59 | \$557,185.41 |
| 100 | Southern California Edison Co., Common | | |
| | Standard Oil Co. of New Jersey, Common | | |
| 100 | Tennessee Gas Transmission Co., 4.60% Cum. Pfd. | | |
| 200 | Tennessee Gas Transmission Co., 4.60% Cum. Pfd. | | |
| 816 | Texas Company, Common | | |
| 400 | Tide Water Oil Co., 1.20 Pfd. | | |
| 300 | Transamerican Corp. | | |
| 225 | Union Carbide & Carbon Corp. | | |
| 75 | Union Carbide & Carbon Corp. | | |
| 290 | U. S. Fidelity & Guaranty Co., (Md.) | | |
| 100 | U. S. Steel Corp., 7% Cum. Pfd. | | |

Total Investments:

| | <i>Endowment Fund</i> | <i>General Fund</i> | <i>Total</i> |
|--------------|-----------------------|---------------------|-----------------------|
| Bonds | \$328,140.39 | \$331,109.68 | \$ 659,250.07 |
| Stocks | 263,891.59 | 557,185.41 | 821,077.00 |
| | <u>\$592,031.98</u> | <u>\$888,295.09</u> | <u>\$1,480,327.07</u> |

OBITUARIES

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

- Dr. Thomas Wade Bennett, F.A.C.P., La Jolla, Calif., March 17, 1959
Dr. Frank Perry Goodwin, F.A.C.P., Jamestown, N. Y., January 16, 1959
Dr. Felix Joel Underwood, F.A.C.P., Jackson, Miss., January 9, 1959
Dr. Redford Alexander Wilson, F.A.C.P., Tucson, Ariz., February 13, 1959

DR. SAMUEL E. ABEL

Dr. Samuel E. Abel, Associate, of Murfreesboro, Tennessee, died in Chicago, Illinois, on April 22, 1959, of heart disease. He was born in New York City, New York, January 27, 1907.

He received his preliminary education in New York City and was granted a B.S. degree at New York University in 1928. He attended New York University College of Medicine, from which he received his M.D. degree in 1931. He interned at Beth Moses Hospital, Brooklyn, New York, from 1931 to 1933. He had postgraduate training at the Veterans Administration Hospital, St. Cloud, Minnesota, in 1939, and at the School of Military Neuropsychiatry in 1945; then trained in internal medicine at the University of Pennsylvania School of Medicine in 1954.

His appointments included Assistant Professor of Clinical Psychiatry at the Vanderbilt University School of Medicine, Nashville, Tennessee; Director of Professional Services, Veterans Administration Hospital, Murfreesboro, Tennessee; and Clinical Assistant, Outpatient Department, Vanderbilt University Hospital.

He entered the Medical Service of the Veterans Administration in February 1939. After a period of psychiatric training at the Veterans Administration Hospital, St. Cloud, Minnesota, he was assigned to the Veterans Administration Hospital, Chillicothe, Ohio, where he served until he entered the military service in 1942. After returning from the Army, he went to the Veterans Administration Hospital, Murfreesboro, Tennessee, where he served excellently in several capacities. The last of these was Director, Professional Services.

He was on active duty with the United States Army from 1933 to 1938, serving in the Civilian Conservation Corps. From 1942 to 1946, he again served in the Medical Corps of the United States Army as Chief of the Neuropsychiatric Service, Fort Hayes, Ohio, and as a Neuropsychiatric Consultant at Lockbourne Army Air Base, Lockbourne, Ohio. He was discharged with the rank of Lieutenant Colonel.

Dr. Abel was a Member of the American Medical Association; a Fellow of the American Psychiatric Association; a Diplomat of the American Board of Psychiatry and Neurology since 1946; and an Associate of the American College of Physicians since 1951.

Dr. Abel is survived by his wife, Mrs. Mary F. Abel of Murfreesboro, Tennessee; a son, Roger, age 23, attending dental college in Memphis, Tennessee; and a daughter, Gertrude, age 20, attending Rice Institute.

WILLIAM S. MIDDLETON, M.D., F.A.C.P.,
Governor for Veterans Administration

DR. JOHN WILLIAM BERRY

On February 23, 1959, Dr. John William Berry, F.A.C.P., died of bronchial asthma. He was born in Denver, Colorado, on August 10, 1914. In 1939 he received an M.D. degree from the University of Colorado School of Medicine. His post-graduate training as intern and resident was accomplished at the Denver General Hospital. For two years he served as an Instructor in Medicine in the Outpatient Department of the Colorado General Hospital and then joined the faculty of the University of Colorado School of Medicine as an Associate Professor of Medicine.

His interests lay in the direction of pulmonary disorders. He was Consultant in Pulmonary Diseases for three years at the Veterans Hospital in Albuquerque, New Mexico, and in 1954 accepted an appointment there as Chief of the Chest Service. He was an Associate Editor, Section on Diseases of the Chest, "Cyclopedia of Medicine, Surgery and the Specialties."

Dr. Berry was a member of the American Medical Association, Colorado State Medical Association, Denver County Medical Society, American Trudeau Society, American Society of Bacteriologists, and American Association for Advancement of Science. He became a Diplomate, American Board of Internal Medicine in 1948 and a Fellow of the American College of Physicians in 1952.

To his widow, Mrs. Priscilla Berry, 3033 Rio Grande Blvd., Albuquerque, New Mexico, the College extends its deep sympathy.

JOHN M. RUMBALL, M.D., F.A.C.P.,
Director, Medical Service,
Veterans Administration

DR. FRANK HARTSUFF BETHELL

Dr. Frank Hartsuff Bethell, F.A.C.P., Professor of Internal Medicine and Director of the Thomas Henry Simpson Memorial Institute for Medical Research of the University of Michigan School of Medicine, died suddenly April 21, 1959. He appeared to be in good health when leaving the train in Ann Arbor on returning from Chicago where he had been in attendance at the Annual Meeting of the American College of Physicians. He apparently succumbed to an acute coronary artery attack before arriving home. He was 56 years of age, having been born on April 11, 1903, in New York City.

Dr. Bethell graduated from Hackley High School in Tarrytown, New York, in 1921 and received the degree of A.B. from Princeton University four years later. He then attended Cambridge University in England for two years followed by two additional years at the Johns Hopkins University School of Medicine, where he received his medical degree in 1929.

After a two-year rotating internship at the Methodist Episcopal Hospital in Brooklyn, New York, Dr. Bethell became associated with the University of Michigan for the next twenty-seven years. Starting as an Instructor in Medicine in 1931, he rose rapidly through various academic positions until his appointment as Professor of Medicine in 1948 and Director of the Simpson Memorial Institute for Medical Research in 1956. In 1940 he was awarded the Henry Russell Award for the excellence of his work as Assistant Professor in 1939. He served from 1943 to 1952 as Medical Director of the Curriculum in Medical Technology. He was a Principal Investigator of the Atomic Energy Commission Project on Biological Effects of Irradiation from 1950 to 1959.

Dr. Bethell was a man of many interests and responsibilities. His principal interest was blood diseases, especially pernicious anemia and related conditions. He regarded himself, however, as an internist with a special interest in hematological disorders. He was a member of many scientific organizations and his bibliography

included over 100 scientific articles. He was a capable investigator and one of his most important studies was a comprehensive investigation of the anemias of pregnancy. Dr. Bethell was an excellent teacher and for five years had complete charge of the course for undergraduate students in clinical laboratory diagnosis. Finally, he had what every physician should have, namely, a thoughtful, kindly interest in and deep concern for his patients.

Dr. Bethell will be greatly missed by his wide circle of friends, including those associated with him at the University of Michigan. His place in the Medical School and Hospital will be difficult to fill.

He is survived by his widow, Mrs. Margaret Krieger Bethell, and two children, Mrs. John L. (Elaine) Vanker, Jr., and David K. Bethell.

CYRUS C. STURGIS, M.D., M.A.C.P.,
Ann Arbor, Michigan

DR. THEODORE RICHARD FAILMEZGER

Dr. Theodore Richard Failmezger, F.A.C.P., died of bullet wounds inflicted by a patient suffering from a mental disorder, on whom he was making a house call. He was killed on February 7, 1959, in Clearwater, Florida.

Born in Brooklyn, New York, on August 20, 1904, he graduated from the New York College of Pharmacy in 1925 with a Ph.G. degree and received a Ph.Ch. degree in 1926 from the Columbia University College of Pharmacy. In 1930 he received a B.S. degree from the Polytechnic Institute of Brooklyn and received his M.D. degree from the Jefferson Medical College of Philadelphia in 1934. He interned at the Orange Memorial Hospital in Orange, New Jersey, 1934-35, and was Resident in Medicine at the New York Post-Graduate Hospital from 1935-36.

Dr. Failmezger began his practice in Madison, New Jersey, in 1936, where he was Physician to the Drew University from 1937 to 1957. He served as President of the Madison Board of Health from 1937-45. His hospital appointments included Member of the Staff of the Orange Orthopedic Hospital and Attending Physician at the All Souls and Morristown Memorial Hospitals from 1938 until 1957.

He was commissioned as a Major in the Medical Corps of the United States Army in 1942 and was promoted to the rank of Lieutenant Colonel. He served as Chief of the Medical Service and later as Commanding Officer of the 116th Station Hospital.

In October, 1957, Dr. Failmezger moved his practice to Clearwater, Florida, where he became a Member of the Staff of the Morton Plant Hospital.

He was a member of the following medical organizations: The American Medical Association; Morris County Medical Society; The Florida Medical Association; the Pinellas County Medical Society; the Florida Society of Internal Medicine; the American Rheumatism Association; the American Geriatrics Association; Kappa Psi, and Omega Upsilon Phi Fraternities; the Elks and Masons, and the Clearwater Methodist Church. He was a Diplomat of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1942.

Dr. Failmezger is survived by his wife, the former Hilda B. Rhinesmith, 809 South Fort Harrison Avenue, Clearwater, Florida, and two sons, George Richard, a law student at the University of Virginia, and Theodore Charles, a freshman of Dartmouth College.

KARL HANSON, M.D., F.A.C.P.,
Governor for Florida

DR. ARTHUR LAWRENCE HOLLAND

Dr. Arthur Lawrence Holland, F.A.C.P., was born in 1873 in Linden, New Jersey, and died on January 20, 1959, of atherosclerosis.

Dr. Holland received his degrees at the New York University Medical College. His academic and hospital appointments were as follows: Assistant Professor of Clinical Medicine, Cornell University Medical College, 1917-1939; Former Consulting Physician, New York Infirmary, Mount Vernon and Elizabeth A. Horton Memorial (Middletown) Hospitals and Consulting Gastroenterologist, New York Hospital. He was forced to give up practice in 1957 due to illness.

He was a member of the following: American Medical Association; Medical Society of the State of New York; New York Academy of Medicine; Greater New York Medical Association; The New York Gastroenterology Society (Past President). He became a Fellow of the American College of Physicians in 1920.

There are no known survivors.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor, Eastern Division
New York State

DR. JOHN WILLIAM HOOKER

Dr. John William Hooker, F.A.C.P., was born August 9, 1914, in Wausau, Wisconsin. He died suddenly while delivering an address at the Bowman Gray School of Medicine of Wake Forest College in Winston Salem, North Carolina, on April 2, 1959.

He received a B.S. degree from Northwestern University in 1934; a B.M. degree from Northwestern University Medical School in 1938 and an M.D. degree from Northwestern University Medical School in 1939. He interned at Presbyterian Hospital, Philadelphia, Pennsylvania, from 1938 to 1940 and had postgraduate training in pathology at the same hospital from 1940 to 1943.

He was Clinical Professor of Pathology, Hahnemann Medical College and Hospital of Philadelphia and its affiliate hospital (Memorial Hospital, Wilmington, Delaware) from 1946 to 1950; Assistant Instructor in Pathology, University of Pennsylvania School of Medicine, from 1941 to 1946, and Pathologist, Memorial Hospital, Danville, Virginia, since 1950.

He was a member of the American Medical Association; American Society of Clinical Pathologists; College of American Pathologists; Virginia State Medical Society; Virginia Society for Pathology, (President, 1955); Philadelphia Pathological Society, (Treasurer, 1949); Virginia Society for Pathology and Laboratory Medicine. He was a Diplomate, American Board of Pathology and a Fellow, American College of Physicians, 1956.

He is survived by his wife, Mrs. John W. Hooker, of 243 Park View Place, Danville, Virginia.

The entire profession in the area where he practiced has sustained a serious loss, for he was not only an able pathologist and teacher but was most effective in co-ordinating clinical medicine with pathology.

CHARLES M. CARAVATI, M.D., F.A.C.P.,
Governor for Virginia

COLONEL HERTEL PHILIP MAKEL

Colonel Hertel Philip Makel, Sr., F.A.C.P. (MC) United States Army (Retired), died in Moorestown, New Jersey, November 7, 1958, from bronchopneumonia. He was born in Baltimore, Maryland, in 1888 and received an A.B. degree from The Johns Hopkins University in 1911, and his M.D. degree from The Johns Hopkins School of Medicine in 1915. After interning at St. Agnes Hospital in Baltimore, 1916-17, he was commissioned in the Medical Corps of the United States Army in May, 1917, and remained in the service until his retirement in 1946 with the rank

of Colonel. He served in France in the American Expeditionary Force from August, 1918, to October, 1919. After returning to the United States, he was Medical Officer at the United States Army Hospital, United States Military Academy, West Point, New York, from 1919-22. He served at the Walter Reed Army Hospital as Assistant Chief of Service from 1922 to 1928. He served as Chief of Surgery Service at the following hospitals from 1929 to 1942: Colon, Christobal, Canal Zone; Fort Totten, New York; Fort Jay, New York; Sternberg General, Manila, Philippines, and Tilton General, Fort Dix, New Jersey. From 1943 until his retirement in 1946, he served as Chief of Professional Services at the Headquarters, 8th Service Command, Dallas, Texas, and 2nd Service Command, Governors Island, New York.

Following his retirement, he established residence at Moorestown, New Jersey.

Colonel Makel was a member of the American Medical Association; the Military Surgeons Association, and of the Phi Gamma Delta Fraternity. He became a Fellow of the American College of Physicians in 1926.

He is survived by his widow, Mrs. Esther S. Makel, 204 Paul Drive, Moorestown, New Jersey; three sons: Dr. Harry P. Makel, San Francisco, California; David D. and John S. Makel, Moorestown, New Jersey, and four grandchildren.

DR. CARL SEEPE NADLER, JR.

Dr. Carl Seepe Nadler, Jr., F.A.C.P., was born on a sugar plantation in Ensenada, Puerto Rico, on June 11, 1917. He died unexpectedly at his home in New Orleans on February 5, 1959.

Dr. Nadler received his preliminary education in Plaquemine and Houma, Louisiana. He obtained his premedical education from the Louisiana State University and then graduated from Tulane University School of Medicine, in June of 1941. He served an internship and residency in internal medicine and cardiology at the Philadelphia General Hospital. He was in the military service from August 1, 1942, to January 28, 1946. He was stationed in Europe and was discharged as a Major.

As a Fellow of the American College of Physicians, an Assistant Professor of Internal Medicine at Tulane, President of the Louisiana State Society of Internal Medicine, a member of the Orleans Parish and Louisiana State Medical Societies, and the American Medical Association, Dr. Nadler was most active, and in his prime of life. He was on the Staff of the Southern Baptist, Touro, Charity, and Eye, Ear, Nose and Throat Hospitals.

Those of us who knew Carl intimately will long remember his hearty laugh, his love of the outdoors, and his devotion to practice and family—a happy combination.

Dr. Nadler is survived by his widow, the former Dr. Rose Anderegg; two daughters, Barbara and Virginia; a son, Carl III; his mother, Mrs. Carl S. Nadler of Donaldsonville; and a brother, William S. Nadler, of Plaquemine, Louisiana.

MARION D. HARGROVE, M.D., F.A.C.P.,
Governor for Louisiana

DR. W. E. RICHARD SCHOTTSTAEDT

It is with regret that we report the death of Dr. W. E. Richard Schottstaedt of Fresno, California. He passed away on January 27, 1959.

Dr. Schottstaedt was born in Brandenburg, Germany, in 1885. He received his A.B. degree in 1907 at the University of Michigan and his M.D. degree at the University of Michigan Medical School in 1909. His practice was confined to Internal Medicine in Fresno, California, where he was respected by his patients and held in high esteem by his associates.

He was a member of the Visiting Staff and Consultant in Medicine, General Hospital of Fresno County since 1921.

During World War I, he was Chairman of Medical Advisory Board; during World War II, he was a member of the Selective Service Board and also Red Cross Director and Chairman of Medical Aid.

He was a member of the American Medical Association; the American Association of Immunologists; the California State Medical Society; the Fresno County Medical Society (President 1930-31); President of the Fresno Board of Education for two terms, and was Past President of the Fresno Kiwanis Club and the Commercial Club. He was a Diplomate of the American Board of Internal Medicine and a Fellow, American College of Physicians in 1928, a Life Member since 1944.

Dr. Schottstaedt is survived by his widow, Mrs. Margaret Swift Schottstaedt, 4269 N. Wilson Avenue, Fresno, California, and two sons.

STACY R. METTIER, M.D., F.A.C.P.,
Governor, Northern California and Nevada

DR. HENRY BARTHELL STEINBACH

Dr. Henry Barthell Steinbach, F.A.C.P., was born on January 22, 1893, in Allimakie, Iowa. He obtained his B.S. degree in 1916 from the State University of Iowa and his M.D. degree from the State University of Iowa College of Medicine in 1920. Postgraduate training was obtained at the Mayo Clinic, Rochester, Minnesota, in 1930.

He carried out his internship and residency in internal medicine at the Grace Hospital, Detroit. He practiced in the field of gastroenterology with Dr. Emerson Vreeland until 1930. At that time Dr. Steinbach transferred his hospital affiliations to Harper Hospital and to Woman's Hospital, Detroit. He expanded his activities to include the entire field of internal medicine with special attention to gastroenterology.

Dr. Steinbach was Extramural Lecturer in the Department of Internal Medicine, University of Michigan Medical School, from 1939-1940; Senior Physician at St. Johns Hospital since 1952, and on the Courtesy Staff of Grace Hospital from 1921 until his retirement in 1957.

Dr. Steinbach served in the Army in World War I. He became a member of the Wayne County Medical Society in 1926. He also held memberships in the American Medical Association, the American College of Cardiology, the American Geriatrics Society, the Michigan State Medical Society and the National Gastroenterological Association. He became a Fellow of the American College of Physicians in 1940 and a Life Member in 1954.

During his entire career, Dr. Steinbach was interested in medical research, and he had the amazing ability to keep abreast of current developments in the medical field, functioning very much as an independent and individual worker. He continued with a keen interest particularly in gastrointestinal research and had established the Henry B. Steinbach Foundation for supporting and furthering medical research.

Dr. Steinbach retired from practice in 1957 and moved to Florida. He died in the Memorial Hospital, New York City, on November 21, 1958, following an operation for brain tumor. He is survived by his wife, Mrs. Edith B. Steinbach, Polo Drive, Gulf Stream, Florida.

H. M. POLLARD, M.D., F.A.C.P.,
Governor for Michigan



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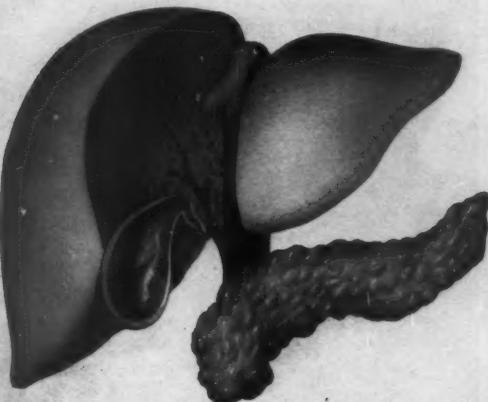
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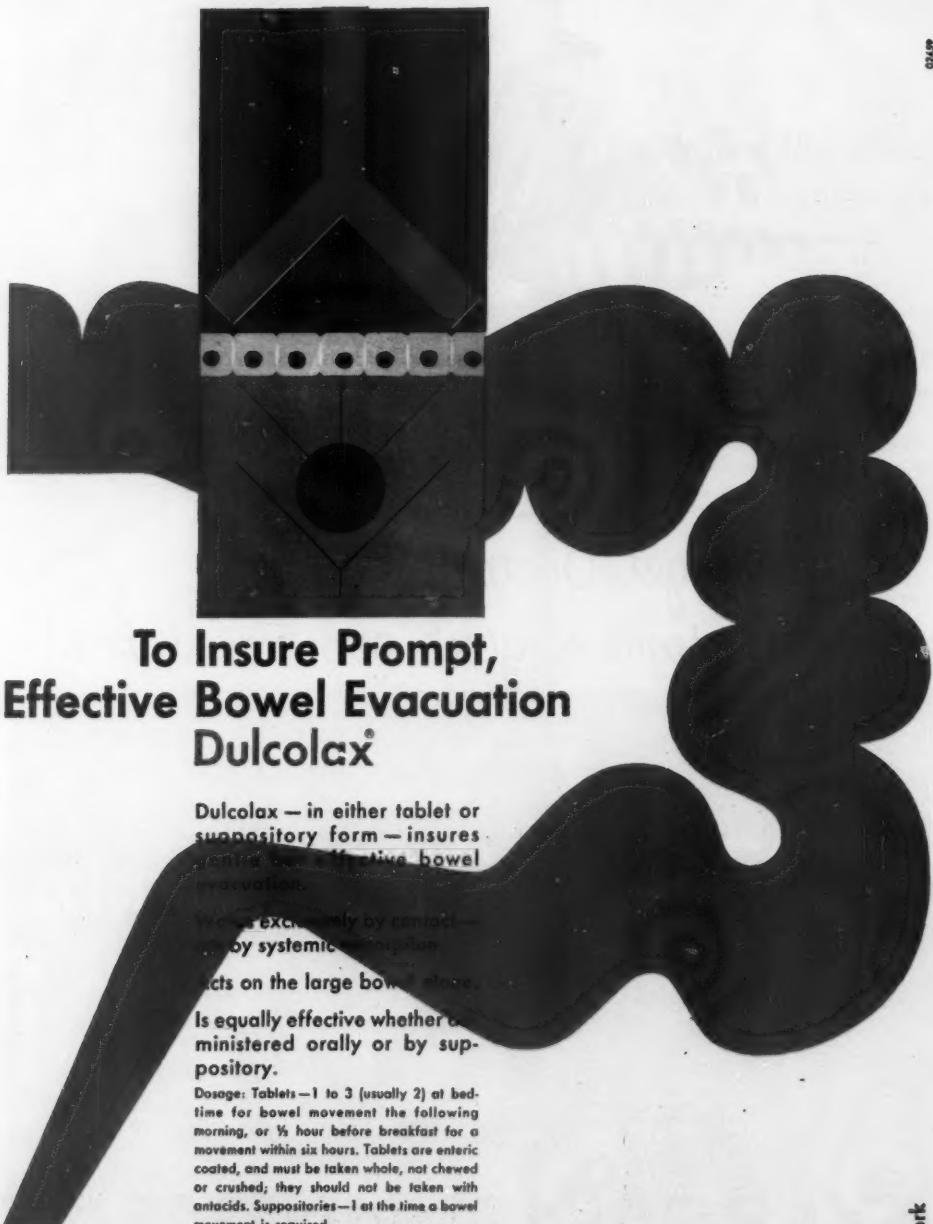
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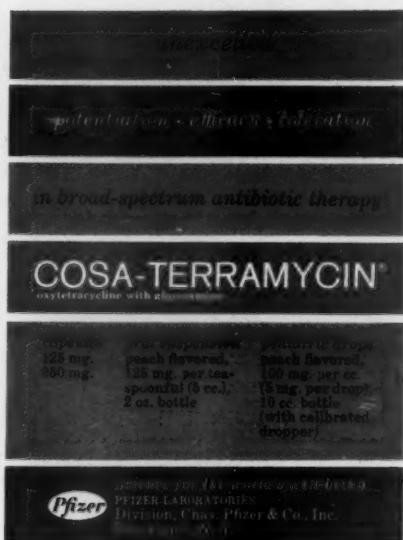
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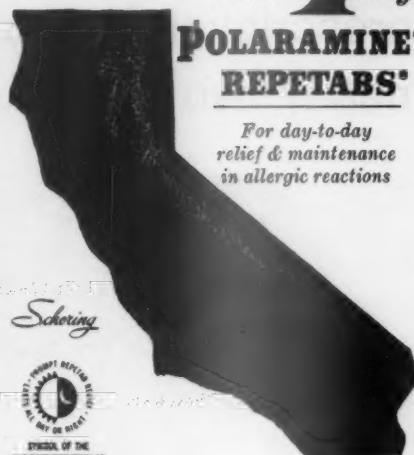
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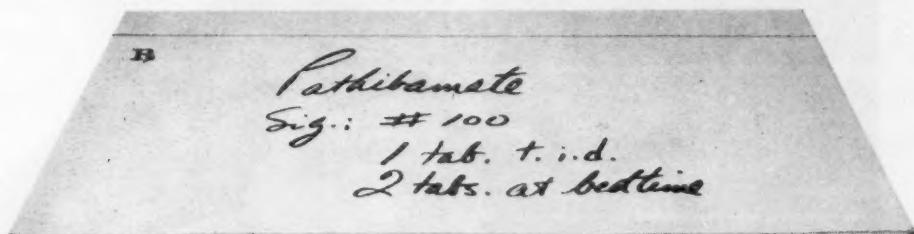
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|-----------------------------|---------------------------------------|------------------------|
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| Gastritis | 16 | 17 |
| Gastroenteritis | — | 55 |
| Colitis | 37 | — |
| Duodenitis | 6 | 3 |
| Functional bowel syndrome | 14 | — |
| Hiatus hernia (symptomatic) | 16 | 1 |
| Pylorospasm or cardiospasm | 11 | 2 |
| Irritable bowel | 11 | — |
| Biliary tract dysfunctions | 11 | 1 |
| Miscellaneous | 7 | 29 |
| Total number of patients | 569 | 156 |

| Clinical Results | Excellent | 150 |
|------------------|-----------|-----|
| Fair | 56 | — |
| Failure | 66 | 6 |

* Oxyphenacyclimine alone—clinically effective in 87% after a year's testing.

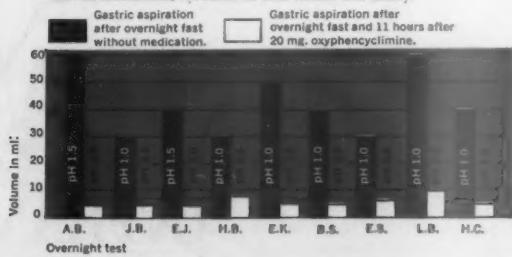
† ENARAX (oxyphenacyclimine plus ATARAX)—all successful cases in "excellent" category.



one tablet at breakfast one tablet at bedtime for full-time relief

ACID REDUCTION AFTER OXYPHENACYCLIMINE THERAPY

Tests conducted in 9 representative ulcer patients after overnight fasts showed considerable reduction in both volume and acidity.



References: 1. Winkelstein, A.: Am. J. Gastroenterol., in press. 2. Leming, B. H.: Proc. Clin. Med. 6:433 (March) 1959. 3. McLaren, G. et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, Calif., January 27, 1958. 4. Strub, L. H., and Carballo, A.: To be published. 5. Data in Roerig Medical Department files. 6. Steigmann, F.: To be published. 7. Schuller, E.: Can. des Hôpitaux 10:391 (Apr. 10) 1957. 8. Farah, L.: Internat. Rec. Med. 169:379 (June) 1956. 9. Harrison, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957.



New York 17, N.Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

when oral tetracycline therapy is impractical—

**AND
SPEED
COUNTS
MEST**



Sumycin Intramuscular provides rapid, sustained antimicrobial activity, when coma, shock, fulminating infection or postoperative complications hamper administration of Sumycin in the oral form. Concentrations in the blood and tissues reach peak levels for immediate control of tetracycline-sensitive organisms in a broad range of infections.

For immediate therapeutic response — Sumycin Intramuscular with Xylocaine.* Single dose vials containing tetracycline phosphate complex (equivalent to 250 mg. tetracycline HCl), and single dose vials containing tetracycline phosphate complex (equivalent to 100 mg. tetracycline HCl).

SUMYCIN

SQUIBB CRYSTALLINE TETRACYCLINE PHOSPHATE COMPLEX
INTRAMUSCULAR

WITH XYLOCAINE*

Flexible dosage forms

| FOR ORAL THERAPY | Tetracycline HCl equivalent (mg.) | Packaging |
|---|-----------------------------------|---|
| Capsules (per capsule)..... | 250 mg. | Bottles of 16 and 100 |
| Half Strength Capsules (per capsule)..... | 125 mg. | Bottles of 16 and 100 |
| Syrup (per 5 cc. teaspoonful)..... | 125 mg. | 60 cc. bottle |
| Aqueous Drops (per cc.)..... | 100 mg. | 10 cc. bottle with "FLEXIDOSIS" dropper |

SQUIBB



Squibb Quality—the Priceless Ingredient

*SUMYCIN® AND "FLEXIDOSIS" ARE DOUGLAS TRADEMARKS. © 1959 ASTRA PHARMACEUTICAL PRODUCTS, INC. FOR LIQUIDS

In peptic ulcer,
five aids to comprehensive management
with 1 preparation

Added to the therapeutic regimen, ALUDROX SA simplifies your comprehensive management of the peptic-ulcer patient. With ALUDROX SA you can relieve the patient's pain, reduce his acid secretion, inhibit gastric motility, calm his emotional distress, and promote healing of his ulcer.

Ambutonium, an important new anticholinergic of demonstrated usefulness, is incorporated in ALUDROX SA to provide potent anti-secretory and antimotility effects without significant side-reactions.

anticholinergic • antacid • sedative • anticonstipant • pepsin-inhibitor

ALUDROX® SA

Suspension and Tablets. Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide, and Butabarbital, Wyeth.



Clinical findings in 900 patients show the selective antihypertensive action of Singoserp

IN 735 PATIENTS, BLOOD PRESSURE FELL AN AVERAGE OF 30.7 mm. Hg:

- more than half of these patients suffered from moderate to severe hypertension
- more than half of the cases involved hypertension of at least 6 years' standing, with many histories of up to 20 years' duration

THE SIDE-EFFECTS PROBLEM WAS MINIMIZED IN MOST PATIENTS:

Chart shows gratifyingly low incidence of side effects in 233 patients given Singoserp with no other antihypertensive medication

| Side Effect | Number | Per Cent |
|------------------------|--------|----------|
| Lethargy | 7 | 2.9 |
| Headache | 6 | 2.5 |
| Gastrointestinal upset | 3 | 1.2 |
| Vertigo | 2 | 0.8 |
| Nasal congestion | 1 | 0.4 |

DOSAGE: Initially, 1 to 2 tablets (1 to 2 mg.) daily.

SUPPLIED: Singoserp Tablets, 1 mg. (white, scored); bottles of 100.

Samples available on request. Write to CIBA, Box 277, Summit, N.J.

remember

Serpasil®
(reserpine CIBA)

for the
anxious
hypertensive
with or
without
tachycardia

**a major
improvement
in rauwolfia**

**a major
advance in
antihypertensive
therapy**

Singoserp®

(syrosingopine CIBA)

2/2007 MK

C I B A
SUMMIT, N.J.



accelerate convalescence with nutritional therapy

Sustagen®

Complete food, Mead Johnson
powder

When you prescribe Sustagen during convalescence, you help fulfill the critical needs of your patients for increased amounts of calories, protein and vitamins. "In some instances of acute illnesses, injury, or surgery, intensive nutritional therapy may be the deciding factor in the outcome."¹ Sustagen, because it generously supplies all known essential nutrients in convenient concentrated form, helps speed recovery.

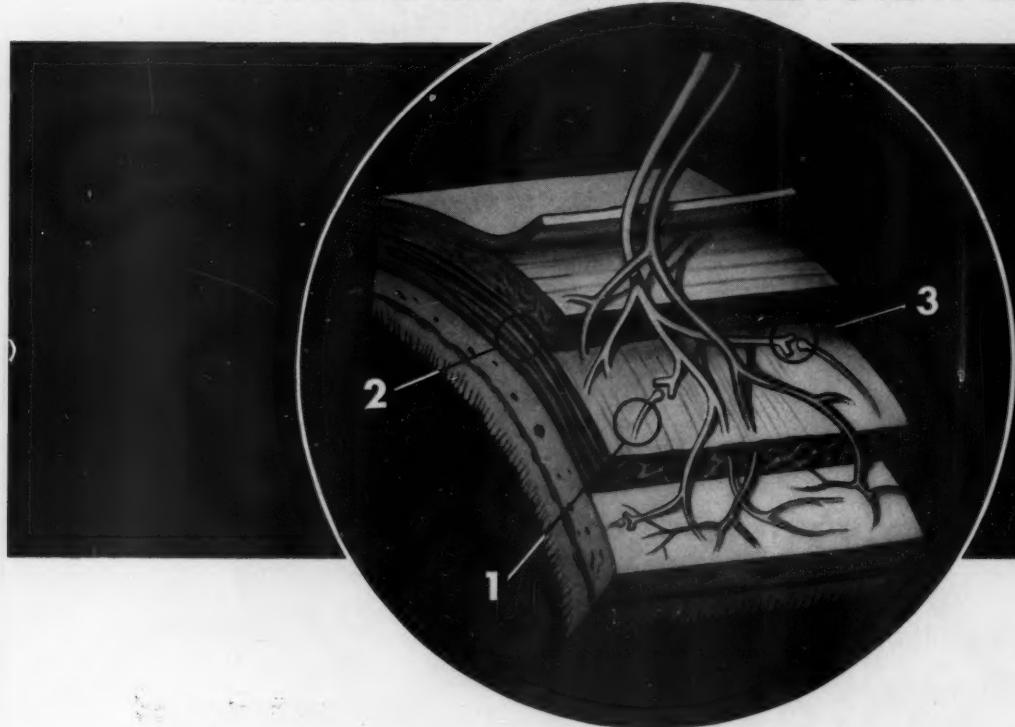


Mead Johnson
Symbol of service in medicine

SU-189M

¹Halpern, S. L.: Ann. New York Acad. Sc. 63: 147-164 (Oct. 20) 1958.

UNIQUE THREE-WAY CONTROL OF SMOOTH MUSCLE SPASM WITH A SINGLE POTENT DRUG



- ① ANTICHOLINERGIC inhibition of parasympathetic stimuli
- ② MUSCULOTROPIC spasmolytic action directly on smooth muscle
- ③ GANGLION-BLOCKING action at synaptic level

"MUREL"®

Brand of Valethamate bromide

IN SMOOTH MUSCLE SPASM

"potent in relaxing the spasm of smooth muscle whether in the G.I., or G.U. tracts, or the gallbladder."¹



in peptic ulcer—breaks the chain reaction of spasm-pain^{2,3}



in G.I. spasm—severe convulsive pain and vomiting reported eliminated or substantially improved without unpleasant side effects or toxic reactions⁴



in biliary spasm and chronic cholecystopathies with or without stones—excellent response promptly achieved⁵



in G.U. spasm—in postoperative spasm, cystitis, and pyelitis, effective relief of pain and spasm was noted in all of a series of 75 patients⁶

Effective and well tolerated . . . "MUREL" provides decisive relief without drug-induced complications; its coordinated three-way action permits significantly low dosage and minimizes reaction potential of any one mechanism; rapidly detoxified and excreted, avoiding cumulative effects. With average therapeutic dosages, there were no side effects such as mouth dryness, visual disturbances, interference with micturition, or bowel evacuation.²

Dosage: Mild to moderate cases: initially, 1 or 2 tablets four times daily. Acute or severe cases: 1 to 2 cc. (10-20 mg.) intravenously or intramuscularly every four to six hours up to maximum of 60 mg. in 24 hour period. The higher dosage range is usually required in spasm of the G.U. and biliary tract.

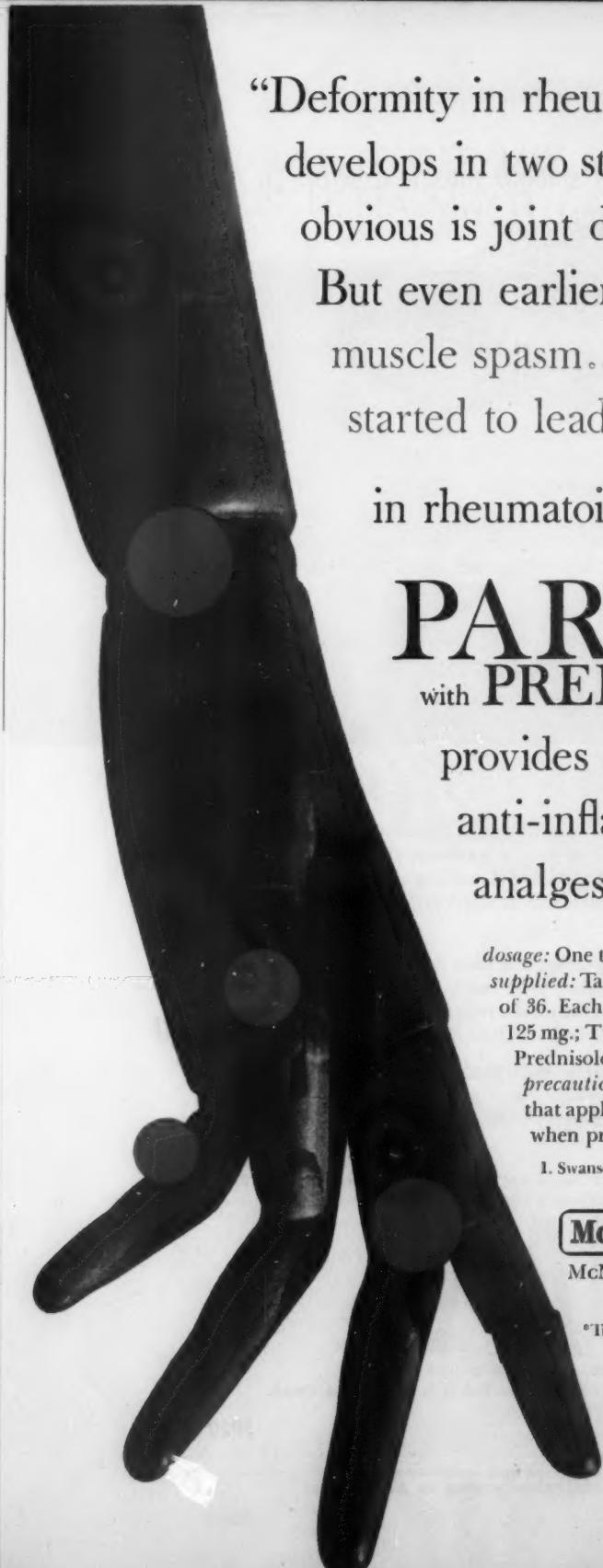
Supplied: "MUREL" Tablets—10 mg. Valethamate bromide, bottles of 100 and 1,000. "MUREL" Injectable—10 mg. per cc., vials of 5 cc. (Also available: "MUREL" with Phenobarbital Tablets—10 mg. Valethamate bromide with $\frac{1}{4}$ gr. phenobarbital per tablet, bottles of 100 and 1,000.)

1. Holbrook, A. A.: Report abstracted in M. Science 4:46 (July 10) 1958. 2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955. 3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955. 4. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.

Ayerst

Ayerst Laboratories New York 16, N. Y. • Montreal, Canada

5920



"Deformity in rheumatoid arthritis develops in two stages. The most obvious is joint destruction.

But even earlier...

muscle spasm...has insidiously started to lead to deformity."¹

in rheumatoid arthritis...

PARAFON*

with PREDNISOLONE

provides spasmolytic,
anti-inflammatory, and
analgesic action

dosage: One to two tablets three or four times a day.

supplied: Tablets, scored, buff colored, bottles of 36. Each tablet contains PARAFLEX® Chlorzoxazone† 125 mg.; TYLENOL® Acetaminophen 300 mg.; and Prednisolone 1.0 mg.

precautions: The precautions and contraindications that apply to all steroids should be kept in mind when prescribing PARAFON WITH PREDNISOLONE.

I. Swanson, J. N.: Canad. M. A. J. 79:638 (Oct. 15) 1958.

McNEIL

MCNEIL LABORATORIES, INC. • PHILADELPHIA 32, PA

*Trade-mark †U.S. Patent Pending



**more dependable absorption for more predictable results in
HYPERTENSION**

Protalba-R contains protoveratrine A,* a single alkaloid of veratrum for more effective management of the hypertensive patient.

Protoveratrine A reduces elevated blood pressure with more predictable results than ever before possible in oral veratrum therapy because of its crystalline purity and ready absorption from the intestinal tract.

Combination of protoveratrine A with crystalline reserpine in Protalba-R permits blood pressure reduction with smaller and thus better tolerated doses than when either drug is used alone.

protalba-R[†]

*Trademark for Tablets Protoveratrine A, 0.2 mg. and Reserpine, 0.08 mg. [†]Patent Pending



PITMAN-MOORE COMPANY Division of Allied Laboratories, Inc., Indianapolis 6, Indiana



combat **HYPOTENSION**

raise and maintain blood pressure with knowledge
that "distressing side effects, such as thrombo-
phlebitis or tissue slough, do not occur."¹

INJECTION

ARAMINE®

(metaraminol bitartrate)

for vasopressor action with a choice of routes

ARAMINE has gained rapid acceptance as a practical vasopressor for combatting hypotension due to hemorrhage and surgical complications. Administer ARAMINE by subcutaneous or intramuscular injection, by intravenous infusion or by direct intravenous injection as the clinical situation demands. Extravascular deposition has not resulted in tissue slough, necrosis or thrombophlebitis.^{1,4} Expect a smooth, sustained vasopressor effect with no secondary fall in blood pressure. There are no reports of tachyphylaxis or hyperglycemia.

ARAMINE is equally valuable in treatment of shock accompanying anaphylaxis, myocardial infarction, brain damage and infectious disease.

supplied: in 1-cc. ampuls and 10-cc. vials (10 mg. per cc.).

references: 1. Circulation 13:834, June 1956.
2. Am. J. M. Sc. 230:357, Oct. 1955.

3. Circulation 16:1096, Dec. 1957.
4. J.A.M.A. 183:1482, April 20, 1957.

ARAMINE is a trademark of Merck & Co., Inc.



MERCK SHARP & DOHME

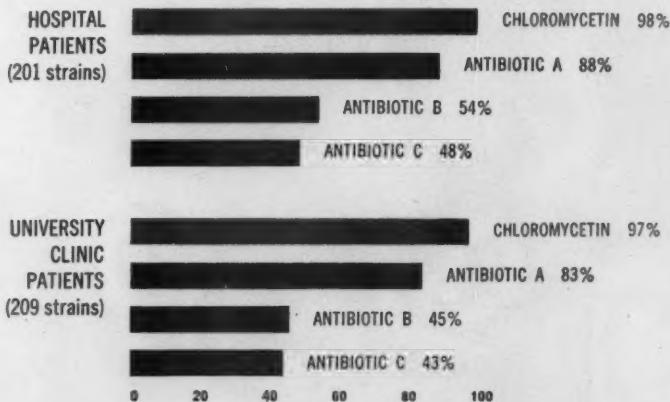
Division of Merck & Co., Inc. Philadelphia 1, Pa.



WHEREVER
STAPHYLOCOCCI
PRESENT
A
PROBLEM

CHLOROMYCETIN®

IN VITRO SENSITIVITY OF STAPHYLOCOCCI, FROM TWO SOURCES,
TO CHLOROMYCETIN AND TO THREE OTHER ANTIBIOTICS*



*Adapted from Fischer, H. G.: *Deutsche med. Wchnschr.* 84:257, 1959.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapsseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

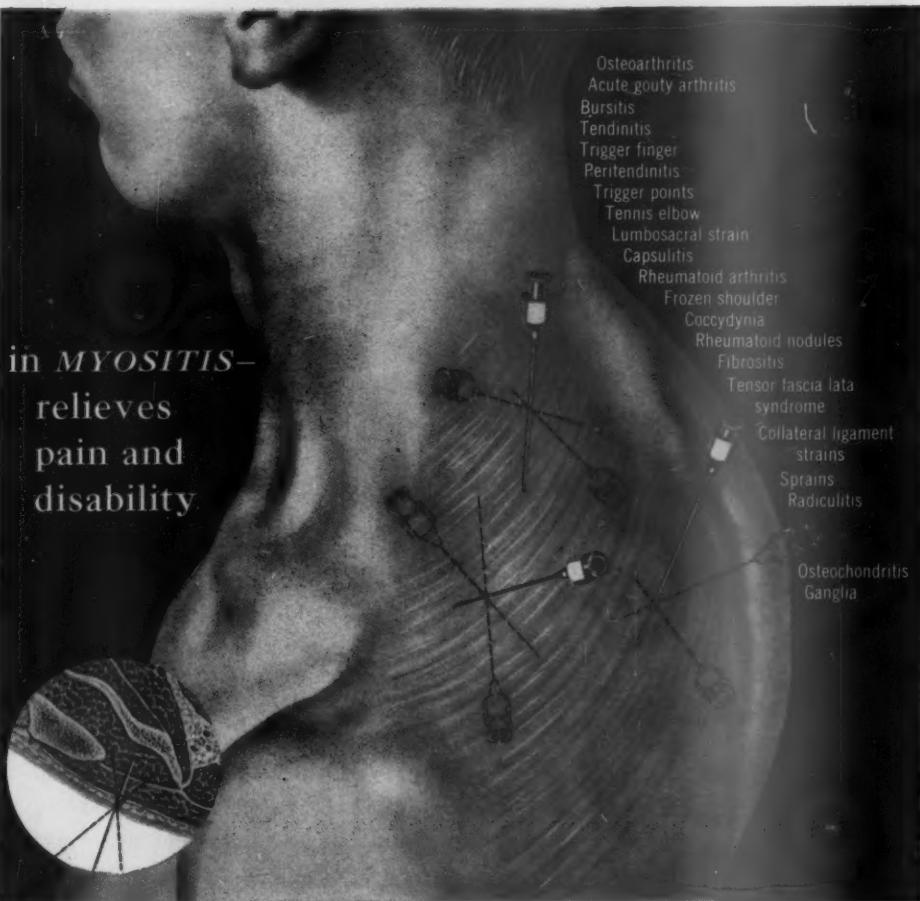


88750

HYDELTRA®-T.B.A.

(Prednisolone tertio-butylacetate, Merck)

for relief that lasts—longer



Anti-inflammatory
effect lasts longer
than that provided
by any other
steroid ester

Hydrocortisone Acetate (6 days—37.5 mg.)

Prednisolone Acetate (8 days—20 mg.)

HYDELTRA-T.B.A.

(13.2 days—20 mg.)



Dosage: the usual intra-articular,
intra-bursal or soft tissue dose
ranges from 20 to 30 mg. depending
on location and extent of
pathology.

Supplied: Suspension "HYDELTRA"
T.B.A.—20 mg./cc. of prednisolo-
ne tertio-butylacetate, in
5-cc. vials.

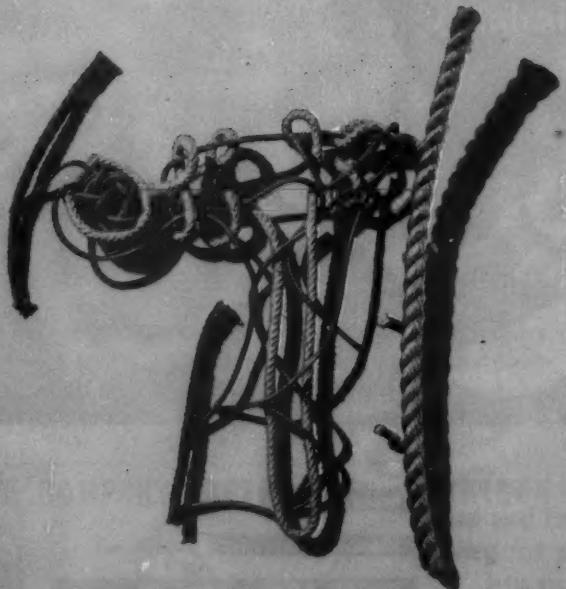


MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

Please Mention this Journal when writing to Advertisers

FURADA

brand of nitrofurantoin



in each patient: 2 million reasons for using FURADANTIN first

pyelonephritis

"the most important concept is that it is a tubular disease"¹

NTIN®

a most important
characteristic:
effective at the
tubular level

*In addition to simple glomerular filtration,
FURADANTIN is actively excreted by the cells of the tubules.*

In the medical management of pyelonephritis, it is important to select an agent such as FURADANTIN which—in addition to its glomerular filtration—is secreted by the cells of the tubules. Sulfonamides, however, both free and acetylated, are excreted primarily by glomerular filtration² and "the mechanism of excretion of tetracycline is solely a glomerular filtration process without tubular involvement."³

Tubular excretion—a significant and singular characteristic of FURADANTIN—is but one reason why "the protracted administration of nitrofurantoin [FURADANTIN] to patients with ineradicable urinary tract infection, particularly chronic pyelonephritis without demonstrable obstruction, may usefully complement the medical management of this difficult problem."⁴

Available as Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

References: 1. Smith, I. M., and Lenyo, L.: Am. Practitioners 9:78, 1958. 2. Bass, A. D.: Chemotherapy of Bacterial Infections II: Sulfonamides, in Drill, V. A., ed.: Pharmacology in Medicine, New York, McGraw-Hill Book Co., Inc., 1954. 3. Pindell, M. H., et al.: J. Pharm. Exp. Ther. 122:61A, 1958. 4. Jawetz, E., et al.: A.M.A. Arch. Int. M. 100:549, 1957.

NITROFURANS—a unique class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK





improved
functional
control

IN PARKINSONISM

Parsidol provides effective and safe control of tremor and muscular rigidity in Parkinsonism.¹ As functional decline is retarded, the increased freedom of movement permits many activities formerly not even attempted.²

Parsidol improves the patient's emotional perspective as his physical coordination and dexterity return. Though effective by itself, Parsidol is also compatible with most other anti-parkinsonian drugs. Side effects are minimal. Most patients respond optimally to a maintenance dosage of 50 mg. q.i.d.

*1. Doshay, L. J. et al.: J.A.M.A. 160:348 (Feb.) 1956
2. Beris, H.: J.Lancet 74:245 (July) 1954.*

PARSIDOL®

brand of ethopropazine hydrochloride





from pollen onset to
... a symptom-

with

METRETON

"METI" STEROID-ANTIHISTAMINIC
TABLETS NASAL SPRAY

METRETON TABLETS

with stress-supportive vitamin C
for systemic therapy intensive enough even
in resistant allergies.

supplied

METRETON® Tablets, bottles of 30 and 100.

Each METRETON Tablet contains 2.5 mg. prednisone,
2 mg. chlorprophenpyridamine maleate, and 75 mg.
ascorbic acid.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

first "killing" frost
controlled summer

Hay fever patients and others with resistant
summer allergies obtain superior relief
from combined "Meti" steroid-antihista-
minic action.

METRETON NASAL SPRAY

for rapid, sustained relief from allergic
nasal symptoms *without* sympathomimetic
or vasoconstrictor side effects.

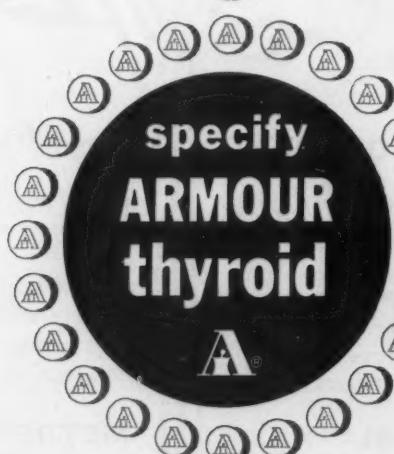
supplied

METRETON Nasal Spray, 15 cc. squeeze bottle.

Each cc. of METRETON Nasal Spray contains 2 mg.
(0.2%) prednisolone acetate and 3 mg. (0.3%) chlorpro-
phenpyridamine gluconate.
Meti® brand of corticosteroids.

Schering

for consistent therapeutic response



specify
ARMOUR
thyroid

pioneer
in thyroid
standardization

*In all conditions requiring substitution
therapy with thyroid hormone*

Supplied in $\frac{1}{4}$, $\frac{1}{2}$, 1, 2 and 5 grain strengths.

ARMOUR PHARMACEUTICAL COMPANY • KANKAKEE, ILLINOIS

A Leader in Biochemical Research

NEW G.I. DOSAGE FORM

FOR DOSAGE ADJUSTABLE TO
THE MEASURE OF THE MAN

Milpath®-200

200 mg. Miltown® + 25 mg. anticholinergic

**1/2 strength Miltown (200 mg.) with
full-level anticholinergic (25 mg.)**

...When the G.I. patient requires *increased anticholinergic effect* with normal levels of tranquilization, prescribe 2 Milpath 200 t.i.d., or as needed.

...When the G.I. patient requires long-term management with established anticholinergic levels but with *lower levels of tranquilization*, prescribe 1 Milpath 200 t.i.d., or as needed.

Two dosage forms of Milpath are now available

MILPATH 200—Each yellow, coated tablet contains 200 mg. meprobamate and 25 mg. tridihexethyl chloride.

DOSAGE: 1 or 2 tablets t.i.d. at mealtime and 2 tablets at bedtime.

MILPATH 400—Each yellow, scored tablet contains 400 mg. meprobamate and 25 mg. tridihexethyl chloride.

DOSAGE: 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

Both forms supplied in bottles of 50 tablets.



WALLACE LABORATORIES New Brunswick, N.J.

FROM MARKED IMPROVEMENT
TO COMPLETE CONTROL
of GRAND MAL SEIZURES

"MYSOLINE"®

wide margin of safety

CLINICAL EVALUATION OF 486
EPILEPTIC PATIENTS* SHOWED THAT:

In patients who had received no previous anticonvulsant medication,

"Mysoline" therapy alone provided marked improvement to complete control of major motor attacks in the majority of patients.

In patients only partially controlled with maximum dosages of other anticonvulsants,
the addition of "Mysoline" therapy was followed by marked improvement to complete control of grand mal attacks in 39% of the patients.

In patients refractory to maximum dosages of other anticonvulsants,

"Mysoline" employed alone provided marked improvement to complete control of major motor attacks in 34% of the patients.

In 39 patients with mixed seizures,
"Mysoline" provided improvement to marked control in 49% of the patients.

The dramatic results obtained with "Mysoline" advocate its use as first choice of effective and safe therapy in the control of grand mal and psychomotor attacks.

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

Literature on request.

*Livingston, S., and Petersen, D.: New England J. Med. 254:327
(Feb. 16) 1956.

5933



AYERST LABORATORIES

New York 16, N.Y.

Montreal, Canada

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries, Ltd.

new for total management of itching, inflamed, infected skin lesions

Mycolog ointment

Kenalog, Spectrocin and Mycostatin in Plastibase

antipruritic / anti-inflammatory / antibacterial / antifungal

Mycolog Ointment — containing the new superior topical corticoid Kenalog — reduces inflammation,^{3,4} relieves itching,^{1,2} and combats or prevents bacterial, monilial and mixed infections.⁵⁻⁷ It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.

"Thirty-one of 38 patients . . . obtained excellent or good control of dermatological lesions . . . [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."⁸

For total management of itching, inflamed, infected skin lesions, Mycolog contains triamcinolone acetonide, an outstanding new topical corticoid for prompt, effective relief of itching, burning and inflammation¹⁻⁴ — neomycin and gramicidin for powerful antibacterial action⁷ — and nystatin for treating or preventing Candida (Monilia) albicans infections.^{8,9}

Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE.

References: 1. Shelimire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nir, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.: Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr., Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957. And whatever the topical corticoid need, a suitable Squibb formulation is available — Kenalog S Lotion — 7½ cc. plastic squeeze bottles. Each cc. supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base and 0.25 mg. gramicidin. Kenalog Cream, 0.1%—5 Gm. and 15 Gm. tubes. Kenalog Lotion, 0.1%—15 cc. plastic squeeze bottles. Kenalog Ointment, 0.1%—5 Gm. and 15 Gm. tubes.



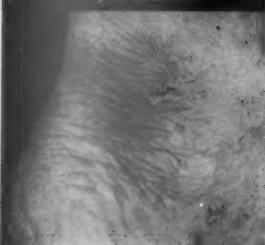
Dermatitis repens (with slaph and monilia) 7 weeks duration



Cleared in 5 days



Infectious eczematoid dermatitis of ankle—5 years duration



Cleared in 20 days



Squibb

Squibb Quality — the Priceless Ingredient

*SPECTROCIN®, **HYDROSTATIN®, *PLASTIBASE®, **HYOGEL®
AND *KENALOG® ARE SQUIBB TRADEMARKS

Compazine® can help you relieve the suffering

brand of prochlorperazine

TENSION HEADACHE



Tension headache is one of many stress symptoms that promptly respond to 'Compazine'.^{1,2,3}

Other symptoms benefited by Compazine's unique nonsedative calming action are functional g.i. complaints, generalized musculoskeletal pain, anorexia and insomnia.

For convenient daylong or nightlong effect with a single oral dose, prescribe 'Compazine' Spansule® sustained release capsules.

Also available: Tablets, Syrup, Suppositories, Ampuls and Multiple dose vials.



SMITH KLINE & FRENCH LABORATORIES, PHILADELPHIA

1. Wennersten, J.R.: Clin. Med. 3:1179 (Dec.) 1956. 2. Settel, E.: J. Am. Geriatrics Soc. 5:827 (Oct.) 1957. 3. McAfoos, L.G., Jr.: Dis. Nerv. System 18:430 (Nov.) 1957.



The advertisement features a vintage electrocardiograph (EK-III) by Burdick. The machine is dark-colored with a control panel featuring several knobs and buttons. Above the machine, the brand name "Burdick" is written in a script font inside an oval. Below the machine, the text "DUAL-SPEED CARDIOGRAPHY" is displayed in bold, uppercase letters. To the left of the machine, the words "for more accurate diagnosis" are written. At the bottom of the advertisement is a stylized illustration of a heart superimposed on a grid of an electrocardiogram tracing.

The importance of dual-speed cardiography is emphasized in this statement from a report* of the Committee on Electrocardiography of the American Heart Association: "It has become increasingly clear that the more or less standard speed of 25 mm. per second incorporated in most instruments makes it difficult on occasion to resolve certain diagnostic details of rapid electrocardiographic deflections." It points out that "a speed of 50 mm. per second appears to be particularly useful."

Weight of the unit is just $22\frac{1}{2}$ lbs., yet the EK-III uses standard-sized

*Circulation, Vol. X, No. 4

THE EK-III
ELECTROCARDIOGRAPH

record paper. The top-loading paper drive eliminates tedious threading. Newly designed galvanometer and rigid single-tube stylus insure maximum record clarity and accuracy.

Investigate the advantages of dual-speed cardiography yourself! Your Burdick dealer will be happy to demonstrate the EK-III at your convenience. No obligation, of course!

THE BURDICK CORPORATION

MILTON, WISCONSIN

Branch Offices:

NEW YORK • CHICAGO • ATLANTA • LOS ANGELES

Dealers in all principal cities

CLINICAL NOTES

HEMATOLOGY

A NEW INTRAVENOUS IRON COMPLEX

ASTRAFER® (ASTRA) I.V.

COMPOSITION A soluble, high-molecular, iron carbohydrate complex, equivalent to 20 mg. trivalent iron per cc., not to be confused with saccharated iron complexes.

PROPERTIES ASTRAFER® I.V. is a neutral solution and does not irritate the intima. It is relatively free from the side reactions previously encountered with other intravenous iron preparations. 70-100% of the iron supplied by this agent is utilized in hemoglobin synthesis. Patient improvement is marked by a measurable sense of well being, and is seen coincidentally with the return to normal of serum iron and hemoglobin levels, usually beginning with the third or fourth injection.

INDICATIONS Severe iron deficiency anemia characteristic of late pregnancy and massive or repeated blood loss, where rapid replenishment of large iron deficits is mandatory, and wherever orally administered iron may be either ineffective or poorly tolerated. To date, there is no evidence that this agent is of any value in anemias of polyarthritis or chronic nephritis. **CONTRAINDICATIONS** are pernicious anemia, leukemia or bone marrow depression, and liver damage.

DOSAGE Initially, 1.5 cc. (30 mg.) to be administered slowly via the intravenous route. Patient should rest 15-30 minutes after each injection. Subsequent dosage increased according to instructions found in literature * accompanying each package.

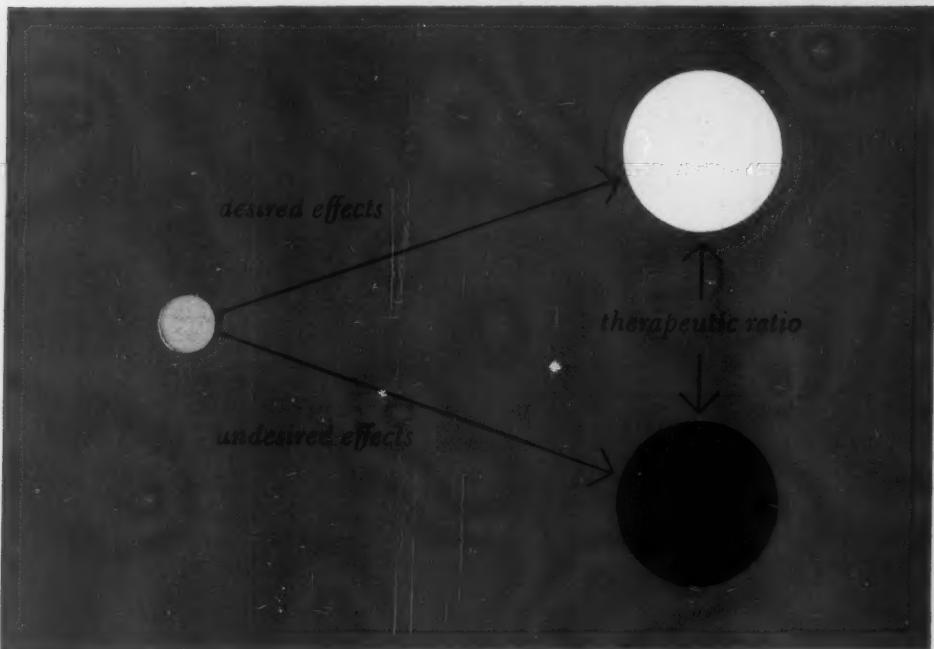
SUPPLIED 5 cc. color-break ampules, boxes of 10

ASTRAFER® (ASTRA) I.V.

*Further information including clinical background and detailed dosage instructions available to physicians on request.

ASTRA PHARMACEUTICAL PRODUCTS, INC.
Worcester, Mass. U. S. A.





**The best therapeutic ratio
in the steroid field**

confirmed by a comparative clinical study of

prednisone
prednisolone
methylprednisolone
triamcinolone
dexamethasone



in 65 rheumatoid arthritis patients:

"... It would appear from these comparative observations that methylprednisolone [Medrol] probably is the steroid of choice for initial trial in a patient with rheumatoid arthritis. It is potent, and displays a slightly improved 'safety' record, showing a reduced frequency of disturbing side effects compared with the other steroids."¹

Medrol
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... hits the disease, but spares the patient

¹. Neustadt, D. H.: Corticosteroid Therapy in Rheumatoid Arthritis: Comparative Study of Effects of Prednisone and Prednisolone, Methylprednisolone, Triamcinolone and Dexamethasone, J.A.M.A., in press.

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*Najarian, J. S., et al.: Am. J. Surg. 96:172, 1958.



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References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958.
2. Robins, H. M.; Lockle, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schafarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

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| | October | November | December | January | February |
|--|----------------------|----------|----------|---------|----------|
| Course No. 1, INTERNAL MEDICINE: Georgetown University School of Medicine, Washington, D. C.; Laurence H. Kyle, M.D., F.A.C.P., Hugh J. Hussey, Jr., M.D., F.A.C.P., and Irving B. Brick, M.D., F.A.C.P., Directors. | X Sept. 28-Oct. 2 | | | | |
| Course No. 2, SELECTED SUBJECTS IN INTERNAL MEDICINE: The University of Buffalo School of Medicine, Buffalo, N. Y.; John H. Talbot, M.D., F.A.C.P., Director. | | | | | |
| Course No. 3, THE SCIENCE OF INTERNAL MEDICINE: State University of New York Upstate Medical Center, Syracuse, N. Y.; Richard H. Lyons, M.D., F.A.C.P., Director. | | | | | |
| Course No. 4, CLINICAL CARDIOLOGY: Tulane University School of Medicine, New Orleans, La.; George E. Burch, Jr., M.D., F.A.C.P., Director. | | | | | |
| Course No. 5, RHEUMATIC DISEASES: Cornell University Medical College and The New York Hospital, New York, N. Y.; Richard H. Freyberg, M.D., F.A.C.P., Director. | | | | | |
| Course No. 6, INTERNAL MEDICINE: Henry Ford Hospital, Detroit, Mich.; John G. Materi, M.D., F.A.C.P., Director. | | | | | |
| Course No. 7, RECENT ADVANCES IN METABOLIC DISEASES: The Mount Sinai Hospital, New York, N. Y.; Alexander B. Gutman, M.D., F.A.C.P., Director. | | | | | |

The following courses are being organized to run simultaneously, March 21-25, 1960; CURRENT CONCEPTS IN CLINICAL GASTROENTEROLOGY; Louisiana State University and Tulane University Schools of Medicine, New Orleans, La.; G. Gordon McHardy, M.D., F.A.C.P., Director. RECENT ADVANCES IN PHARMACOTHERAPY; University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director. The following course is scheduled for April 25-29, 1960: DERMATOLOGY FOR THE INTERNIST; University of Michigan Medical School, Ann Arbor, Mich.; Arthur C. Curtis, M.D., F.A.C.P., Director.

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1. Shock in myocardial infarction, *Heart Bull.* 6:107, Nov.-Dec., 1957. 2. Agress, C. M.: *Am. J. Cardiol.* 1:231, Feb., 1958. 3. Garai, Oliver, and Smith, K. S.: *Brit. M. J.* 1:247, Feb. 1, 1958.
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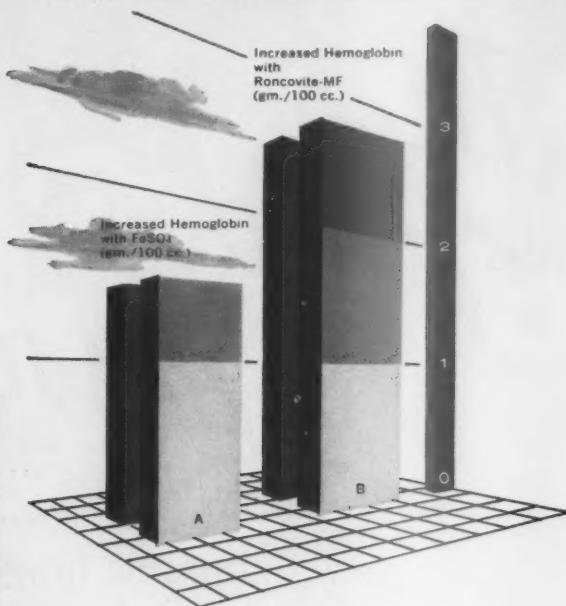
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